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Projections From the Amygdala to Basoventral and Mediodorsal Prefrontal Regions in the Rhesus Monkey

H. BARBAS AND J. DE OLMOS

Department of Health Sciences, Boston University, and Department of Anatomy and Neurobiology, Boston University School of Medicine, Boston, Massachusetts 02215 (H.B.) and Instituto de Investigación Médica, "Mercedes y Martin Ferreya," Cordoba, Argentina (J.D.O.)

ABSTRACT

The sources of ipsilateral projections from the amygdala to basoventral and mediodorsal prefrontal cortices were studied with retrograde tracers (horseradish peroxidase or fluorescent dyes) in 13 rhesus monkeys. The basoventral regions injected with tracers included the orbital periallocortex and proisocortex, orbital areas 13, 11, and 12, lateral area 12, and ventral area 46. The mediodorsal regions included portions of medial areas 25, 32, 14, and dorsal area 8. The above sites represent areas within two architectonic series of cortices referred to as basoventral or mediodorsal on the basis of their anatomic location. Each series consists of areas that show a gradual increase in the number of layers and their delineation in a direction from the caudal orbital and medial limbic cortices, which have an incipient laminar organization, towards the eulaminated periarcuate cortices (Barbas and Pandya, J. Comp. Neurol. 286:353–375, '89).

Labeled neurons projecting to the prefrontal cortex were found in the basolateral, basomedial (also known as accessory basal), lateral, and ventral cortical nuclei, and in the anterior amygdaloid and amygdalopiriform areas. The distribution of labeled neurons differed both quantitatively and qualitatively depending on whether the injection sites were in basoventral or mediodorsal prefrontal cortices. Cases with caudal orbital injections had the most labeled neurons in the amygdala, followed by cases with injections in cortices situated medioventrally. The latter received a high proportion of their amygdaloid projections from the basomedial nucleus. The lateral amygdaloid nucleus sent a robust projection to the least architectonically differentiated orbital periallocortex, and a weaker projection to the adjoining orbital proisocortical regions, but did not appear to project to either medial proisocortical sites or to the more differentiated ventrolateral or dorsolateral prefrontal cortices. In addition, there were topographical differences in the origin of projections from one amygdaloid nucleus directed to various prefrontal cortices. These differences were correlated either with the destination of the axons of afferent amygdaloid neurons to basoventral or to mediodorsal prefrontal cortices and/or with their projection to areas with varying degrees of laminar organization within the basoventral or mediodorsal sector. The clearest topography was observed for projections originating in the basolateral nucleus. The results indicate that the least architectonically differentiated basal sites situated in the caudal orbitofrontal region, followed by the comparable medial areas situated ventrally on the medial surface, received the strongest and most widespread projections from the amygdala. Medial proisocortices situated more dorsally and caudally received only a few projections from the amygdala. In addition, areas with a high degree of laminar organization (caudal areas 46 and 8) within both basoventral and mediodorsal regions received few and topographically restricted amygdaloid projections.

Key words: prefrontal architecture, limbic system, cortical architecture, memory, macaque monkeys

Situated deep in the temporal lobe, the amygdala is composed of a heterogeneous group of nuclei (Fig. 1). It is connected with several cortical systems including visual, auditory, somatosensory and frontal (Whitlock and Nauta,

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Address corresspondence to H. Barbas, Department of Health Sciences, Boston University, 635 Commonwealth Avenue, Room 431, Boston, MA 02215.

'56; Nauta, '61; Pandya et al., '73; Herzog and Van Hoesen, '76; Jacobson and Trojanowski, '75; Potter and Nauta, '79; Aggleton et al., '80; Van Hoesen, '81; Mufson et al., '81; Porrino et al., '81; Amaral and Price, '84). The role of the anatomic interactions between the amygdala and the cortex is not known even though the amygdala has been implicated in some aspects of mnemonic processes (Mishkin, '78; Zola-Morgan et al., '82; Saunders et al., '84).

Like the amygdala, the prefrontal cortex receives projections from cortices associated with several sensory modalities and from the amygdala (Barbas, '90; De Olmos, '90, for reviews). However, there is little information on the organization of amygdaloid afferent projections from distinct prefrontal zones (Amaral and Price, '84). This information is important in view of recent studies showing that subsectors of the prefrontal cortex have different anatomic and functional attributes. For example, using architectonic criteria, the prefrontal cortex has been subdivided into two sectors identified as basoventral or mediodorsal on the basis of their anatomic location (Barbas and Pandya, '89; Fig. 2). Basoventral and mediodorsal prefrontal cortices have different intrinsic (prefrontal) and post-Rolandic connections (Barbas, '88b; Barbas and Pandya, '89) and are characterized by distinct physiologic and behavioral properties (Petrides, '82; Vaadia et al., '86; Bachevalier and Mishkin, '86). This information implicates basoventral prefrontal areas in the processing and/or storing of stimulus features. On the other hand, mediodorsal regions may be involved in spatial functions and spatial memory (Pandya and Yeterian, '85; Goldman-Rakic, '88; Barbas, 1988b). There is little information on the relationship of amygdaloid projections to each of these two groups of prefrontal cortices, an issue addressed in the present study.

In a second question we asked whether there are differences in the relative density and topography of amygdaloid projections directed to distinct architectonic zones within the basoventral or mediodorsal prefrontal cortices. This question is based on the observation that each of the two prefrontal sectors is composed of a series of regions characterized by different degrees of laminar organization. Within the basoventral or the mediodorsal sector, the least architectonically differentiated areas are the limbic, which have three or fewer layers (Barbas and Pandya, '89). The limbic areas give way to successively adjacent isocortical areas that exhibit stepwise increases in the number of layers and in their delineation. On the basoventral surface gradual increases in laminar organization can be traced in a direction away from the limbic cortices in the caudal orbitofrontal region (periallocortex and proisocortex), through a series of adjacent rostral orbital and then ventrolateral areas towards the ventral periarcuate region. Similarly, on the mediodorsal surface the least architectonically differentiated areas are the limbic periallocortex and the proisocortices (areas 24, 25, and 32) found around the rostral portion of the corpus callosum. A gradual increase in laminar organization is observed through adjacent medial and then dorsolateral areas towards the dorsal periarcuate region (Fig. 2). The present study sought to determine which prefrontal cortices are connected preferentially with the amygdala and whether there are topographic differences in the origin of amygdaloid projections directed to cortices with different degrees of laminar organization within the basoventral or the mediodorsal prefrontal cortices.

METHODS

Experiments were conducted on 13 rhesus monkeys (*Macaca mulatta*), anesthetized with ketamine hydrochloride (10 mg/kg, i.m.) followed by sodium pentobarbital administered intravenously through a femoral catheter until a surgical level of anesthesia was achieved. Additional anesthetic was administered during surgery as needed. Surgery was performed under aseptic conditions. The monkey's head was firmly positioned in a holder that left the cranium unobstructed for surgical approach. A bone defect was made, the dura was retracted, and the cortex was exposed.

Horseradish peroxidase (HRP) experiments

In 11 animals injections of a solution containing 8% HRP conjugated to wheat germ agglutinin (Sigma Chemical Co.,

Abbreviations

A	arcuate sulcus
AAA	anterior amygdaloid area
AC	anterior commissure
ACo	anterior cortical nucleus
AHA	amygdalo-hippocampal area
APir	amygdalopiriform area
b	fast blue
BL	basolateral nucleus
BM	basomedial nucleus
C	central sulcus
Ca	calcarine fissure
CC	corpus callosum
Ce	central nucleus
Cg	cingulate sulcus
Cl	claustrum
H	hippocampus
INS	insula
IO	inferior occipital sulcus
IP	intraparietal sulcus
IS	injection site
L	lateral nucleus
LF	lateral fissure
LO	lateral orbital sulcus
Me	medial nucleus
MO	medial orbital sulcus
MPO	medial parietooccipital sulcus
O12	orbital area 12
OLF	olfactory area
OP	operculum
OT	occipitotemporal sulcus
P	principal sulcus
PAll	periallocortex
Pro	proisocortex
ProM	proisocortical motor area
PCo	posterior cortical nucleus
PL BL	paralamellar basolateral nucleus
PO	parietooccipital sulcus
R	rhinal sulcus
r	rhodamine
Ro	rostral sulcus
s46	sulcal 46 (ventral)
ST	superior temporal sulcus
STR	striatum
V	ventricle
VCo	ventral cortical nucleus
VCo If	inferior division of ventral cortical nucleus
VCo It	intermediate division of ventral cortical nucleus
VCo S	superior division of ventral cortical nucleus
y	diamidino yellow

St. Louis, MO) were made with a microsyringe (Hamilton, 5 μl) mounted on a microdrive which was attached to a carrier (Kopf). The needle was lowered to the desired site under microscopic guidance. Small amounts (0.05 μl) of the injectate were delivered 1.5 mm below the pial surface at each of two adjacent sites separated by 1–2 mm over a 30-minute period. The basoventral prefrontal regions injected with HRP included the orbital periallocortex and proisocortex, orbital area 12, and ventral area 46. The orbital periallocortex and proisocortex are situated behind Walker's ('40) area 13 and are not included in his map. Orbital area 12 and area 46 correspond to the regions designated by the same numbers in Walker's ('40) map. The mediodorsal regions included medial areas 25 and 32, and dorsal area 8. The latter is within Walker's ('40) area 8. Medial area 32 is within an area designated by the same number in the map of Brodmann ('05). Area 25, as parcelled recently, occupies a region below the rostrum of the corpus callosum (Vogt et al., '87). A composite of the injection sites is shown in Figure 2.

Following a 40–48 hour survival period the monkeys were re-anesthetized and perfused through the heart with saline until the blood was cleared. A timed fixation procedure then followed, during which 2 liters of fixative (1.25% glutaraldehyde, 1% paraformaldehyde in 0.1 M phosphate buffer at pH 7.4) were delivered over a 30-minute period. The fixative was followed by perfusion with 2 liters of cold (4°C) phosphate buffer (0.1 M, pH 7.4).

The brain then was removed from the skull, photographed, and placed in glycerol phosphate buffer (10% glycerol and 2% DMSO in 0.1 M phosphate buffer at pH 7.4) for 1 day and in 20% glycerol phosphate buffer for another 2 days. The brain then was frozen in −75°C isopentane as described by Rosene et al. ('86) and transferred to a freezing microtome. Sections were cut in the coronal plane at 40 μm in ten series and collected in a solution of 0.1 M phosphate buffer (pH 7.4). One series of sections was treated for the visualization of HRP according to a procedure in which tetramethyl benzidine is used as the chromogen (Mesulam et al., '80). The tissue was mounted, dried, and counterstained with neutral red. Adjacent series of sections were stained for the visualization of Nissl bodies, myelin, acetylcholinesterase, or cytochrome oxidase to aid in delineating architectonic borders (Geneser-Jensen and Blackstad, '71; Gallyas, '79; Wong-Riley, '79).

Fluorescent tracer experiments

With the aid of the surgical procedures outlined above, two animals received injections of fluorescent tracers (FT). In one of these animals (case 3) an injection of fast blue (3%, 0.4 μl) was placed in area 13 (case 3b), diamidino yellow (3%, 0.4 μl) was placed in orbital area 12 of Walker ('40) and Barbas and Pandya ('89) (case 3y), and an injection of rhodamine-labeled fluorescent microspheres (0.5 μl, in suspension provided by the manufacturer) was placed in area 32 (case 3r). In another animal (case 11), an injection of fast blue (3%, 1 μl) was placed in the caudal part of medial area 14 (case 11b) and an injection of diamidino yellow (3%, 0.5 μl) was placed in area 32 (case 11y). After a survival period of 10 days the animals were deeply anesthetized and perfused with 6% paraformaldehyde in 0.1 M cacodylate buffer at pH 7.4. The brain then was placed in a solution of 6% paraformaldehyde with 10% glycerol and 2% DMSO for 1 day and transferred to a solution containing 20% glycerol in 2% DMSO for another 2 days. The brain then was frozen, cut in the coronal plane at 40 μm, and the sections mounted on subbed slides.

Data analysis

Brain sections prepared according to the methods described above were viewed microscopically under bright- and dark-field illumination for HRP cases, or fluorescence illumination for cases 3 and 11. Drawings of brain sections through the amygdala, the location of labeled neurons ipsilateral to the injection site, and the site of blood vessels used as landmarks were transferred from the slides onto paper using a digital plotter (Hewlett Packard, 7475A), which is electronically coupled to the stage of the microscope and to a computer (Compaq 386). Movement of the stage of the microscope is recorded via linear potentiometers (Vernitech) mounted on the X and Y axes of the stage of the microscope and coupled to a power supply. Each labeled neuron is recorded by aligning the center of a cross hair (inserted permanently in one eyepiece of the microscope) with the center of the labeled neuron and pressing a button (on the mouse) to record its presence. The analog signals are converted to digital signals via an analog-to-digital converter (Data Translation) in the computer. Software developed in this laboratory allow each labeled neuron noted by the experimenter to be recorded only once. This procedure allows us to draw the outline of the amygdala by moving the stage of the microscope using the cross hair as a reference and to record the location of labeled neurons with respect to anatomic landmarks accurately. An example of a section through the amygdala plotted using this system is shown in Figure 3F.

All of the prepared slides through the amygdala in one series were examined, and all sections containing labeled neurons were charted. Labeled neurons (represented as dots on the charted sections) were counted by outlining the area of interest (e.g., one nucleus), as described above. The number of labeled neurons within the enclosed area was calculated using an algorithm written for this purpose. An identified region, which outlined a particular nucleus and could have any shape, was then subdivided automatically along its dorso-ventral or medio-lateral extent into five sectors and the number of labeled neurons per sector recorded. Labeled neurons in each dorso-ventral or medio-lateral sector were then counted in serial sections. This feature of the program allowed for a more detailed topographic analysis. To evaluate the topography of labeled neurons within the rostro-caudal extent of a given nucleus, sections through the amygdala in which the nucleus was present were counted and the number divided by five. The number of labeled neurons in each rostro-caudal sector through a particular nucleus was then calculated.

Procedural variables, such as size of the injection site, exposure of the tissue to alcohol, etc., inadvertently differ from case to case. To minimize the above extrinsic factors, the relative afferent input to the injected site from a particular amygdaloid nucleus was assessed by expressing the number of labeled neurons in serial sections through that nucleus as a percentage of the total number of labeled neurons in the entire amygdala in that case. This analysis is based on the assumption that retrograde transport and histochemical variables underlying HRP or fluorescent dye sensitivity affect all amygdaloid nuclei in that case in a similar manner. It is possible then to demonstrate the projection profile of each case and some qualitative differences in the pattern of regional labeling among cases.

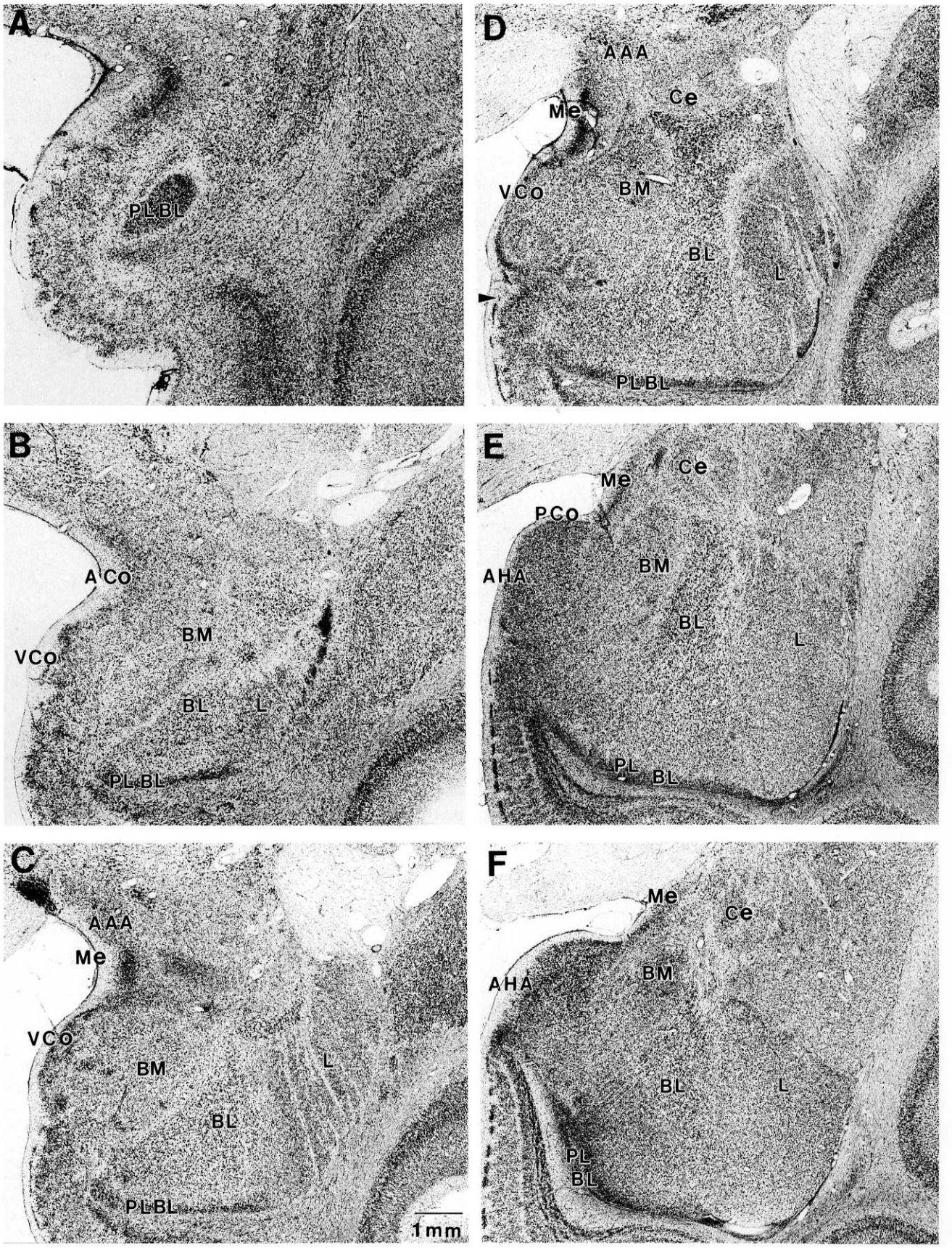
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Figure 1

Reconstructions

The cortical regions containing the injection sites were reconstructed serially using the sulci as landmarks and are shown on diagrams of the surface of the cortex. The latter were drawn from photographs of each brain showing the external morphology of the experimental hemispheres. The drawings were modified to represent the relative location of the injection sites within banks of sulci. In some cases the injection sites were depicted on unfolded maps of the prefrontal cortex. The maps were prepared using a method that we described recently (Barbas and Pandya, '87, '89; Barbas, '88b). Briefly, the unfolded maps were prepared by measuring the depth of sulci and exposed cortex through layer IV from coronal sections. The length of sulci and gyri for each rostrocaudal level was proportionally depicted in a straight line. The circular cortex, therefore, is represented on a flat surface by inserting an artificial cut between the medial and basal surfaces (Fig. 2D, extreme top and bottom of map).

The constructed map contains a "fixed" axis that depicts the rostrocaudal dimension of the brain (shown from right-to-left in Fig. 2D). The other axis is variable and shows the extent of the unfolded cortex in a series of rostrocaudal points (depicted from top to bottom in Fig. 2D). Because the dorsoventral axis varies in length as the extensive cortex buried in sulci is unfolded, the finished map appears elongated, and sulci that are the furthest from the reference point may appear distorted. For a better visual representation of the unfolded map, the rostrocaudal dimension was expanded by a factor of 2.5 in the diagrams. As discussed previously, this method of unfolding the cortex introduces some visual but very little areal distortion (3 ± 2%). References to architectonic areas of the prefrontal cortex are according to the classification of Barbas and Pandya ('89).

Amygdaloid borders

Architectonic boundaries of amygdaloid nuclei containing labeled neurons were determined from series of matched sections stained with thionin, myelin, acetylcholinesterase, or cytochrome oxidase using as a basis differences in cytoarchitecture and the differential distribution of the enzymes (Figs. 1, 3). The borders of amygdaloid nuclei were placed first on photographs of these matched series of sections and then onto photographs of the sections containing labeled neurons and the charted drawings by using blood vessels as landmarks (Fig. 3A,B,C,F). The photographs were obtained by placing glass slides with mounted tissue on a photographic enlarger and projecting a negative image directly onto photographic paper (Kodak, panchromatic; Fig. 3A–C).

Amygdaloid terminology

The terminology for the amygdala used in this study is based largely on the studies of Johnston ('23), and complemented when necessary with the nomenclature of Brockhaus ('40) and De Olmos ('90) for the human amygdala, and Price ('81) and Price et al. ('87) for the macaque monkey. In a comparative study Johnston ('23) subdivided the amygdala in the opossum, rat, rabbit, bat, macaque monkey, and in human embryos. Johnston's terminology for macaque monkeys and human embryos is consistent with what he proposed for other nonprimate mammals, a procedure that was followed only partially by Crosby and Humphrey ('41) for the human amygdala, and later by Lauer ('45) in the macaque monkey. The major point of controversy concerns portions of the basal amygdaloid complex, which in the rat comprises the basomedial, basolateral, and lateral nuclei (De Olmos et al., '85; De Olmos, '90, for reviews). Johnston named the most dorsal and medial portion of the basal group the "medial basal" nucleus in primates. In an unexplained departure from Johnston's original account, Lauer ('45) used the name "accessory basal" for the same nucleus. Johnston ('23) reserved the name "accessory basal" for a different nucleus, which he claimed was present only in the opossum among the species he had examined (see also Young, '36 for the rabbit, and Fox, '40 for the cat). Mehler's ('80) hodological studies in macaque monkeys led us to suggest that the accessory basal nucleus of primates described by Lauer ('45) would be at least in part homologous to the basomedial nucleus in the rat and cat, a possibility that was also entertained by Price ('81) and Amaral ('85). Moreover, Price suggested that in the monkey the parvicellular portion of the adjacent "basal" nucleus (Bpc in his terminology) is homologous to the smaller-celled part of the basolateral nucleus in the rat and cat (see also Amaral, '85; Price et al., '87). Amaral ('85) suggested further that the entire "basal" nucleus in primates may be homologous with the basolateral nucleus in nonprimates. On the basis of the above considerations, and in agreement with previous discussions on this topic (Koikegami, '63; De Olmos, '90), it seems reasonable to retain the earlier terminology of Johnston ('23) with regard to the most medial and dorsal member of the basal nuclear group (basomedial, BM) and to consider the adjacent nucleus (including the ventromedially situated parvicellular group of cells) as the basolateral (BL) nucleus (Figs. 1, 3A,B,C). This classification is consistent with the atlas of the amygdala in *Macaca fuscata* according to the map of Kusama and Mabuchi ('70) and with the nomenclature used for the human amygdala according to Brockhaus ('40), Nitecka and Narkiewicz, ('76), and De Olmos ('90).

Our terminology for the cortical amygdaloid group requires some explanation as well. In the present account we recognize the existence of anterior (ACo) and posterior (PCo) sectors of the cortical nucleus as described by Price et al. ('87). Based on this recent parcelling of the cortical nucleus, Johnston's ('23) cortical amygdaloid nucleus, however, appears to lie medioventral to both ACo and PCo, and we thus use the name ventral cortical (VCo) to distinguish it from the other subdivisions (Fig. 1). The VCo does not seem to encompass the region variously designated the corticoamygdaloid transition area (Crosby and Humphrey, '41, '44; Lauer, '45), or the amygdalopiriform (APir) area (Humphrey, '68). However, the "periamygdaloid cortex" of some other authors (Rose, '27; Koikegami, '63; Mikami, '52; Price et al., '87) includes both VCo and APir. We distinguish between these two regions because thymidine autoradiographic studies in the rat show developmental features consistent with those of a subcortical nuclear group formation for VCo (Bayer, '80). In addition, maturation of APir seems to precede that of surrounding struc-

Fig. 1. Brightfield photomicrographs of coronal sections from rostral (**A**) through caudal (**F**) sectors of the amygdala showing the location of the various nuclei and their cytoarchitecture. These sections were taken from case 3. Arrowhead in D points to APir area. (Frozen cut tissue, cresyl violet stain; scale bar = 1 mm.)

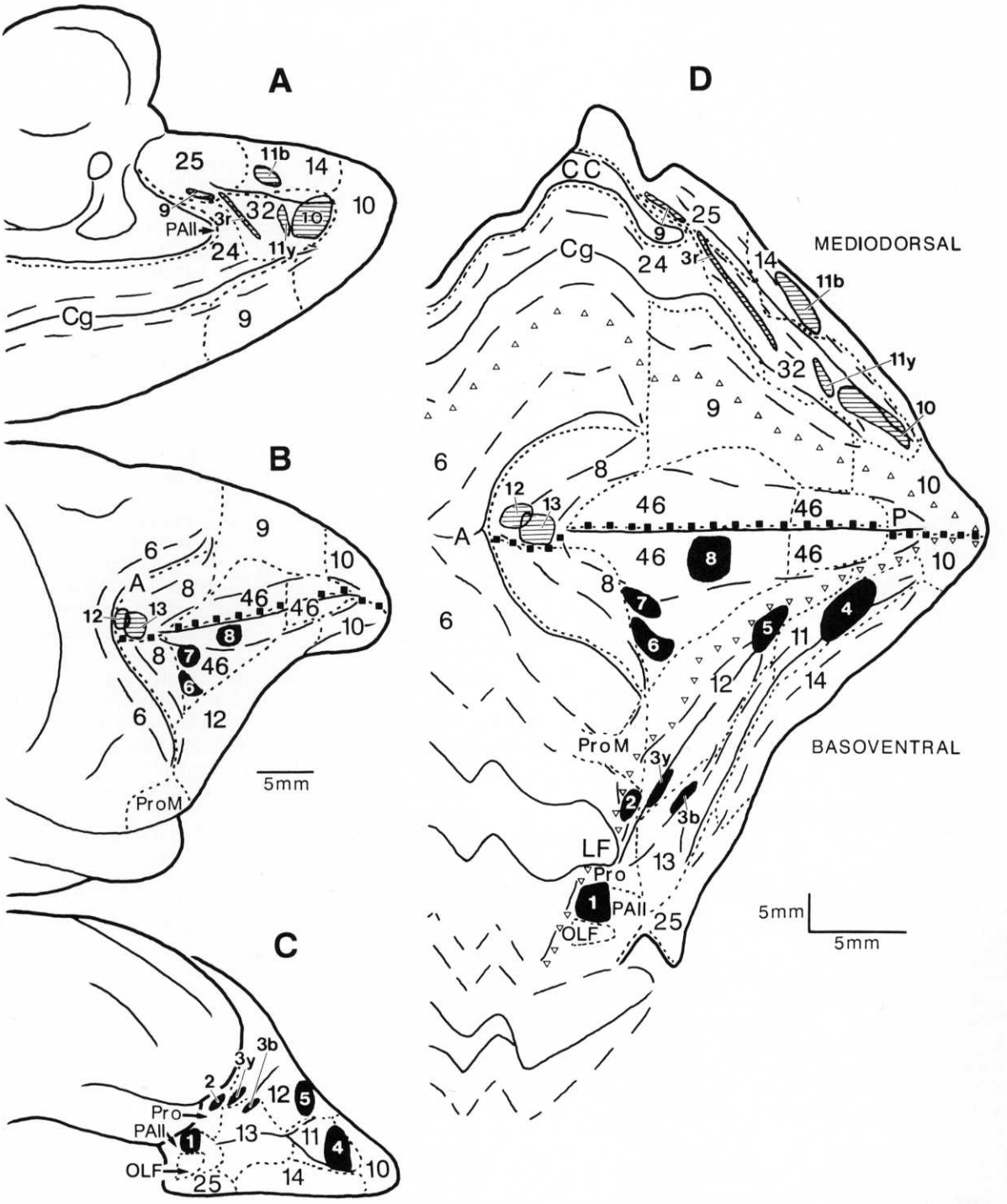

Fig. 2. Composite of injection sites shown on the medial (**A**), lateral (**B**), and basal (**C**) surfaces of the cerebral hemisphere, and on a map where the sulci were unfolded (**D**). The injection sites are superimposed on an architectonic map of the prefrontal cortex (Barbas and Pandya, '89). Mediodorsal areas appear above and basoventral below the heavy line (squares in B, D). Within the mediodorsal sector, stepwise increases in laminar organization are observed in a direction from the medial periallocortex (PAll) to proisocortical areas 24, 25, and 32, and then through medial areas 14, 10, and 9, to dorsal areas 9, 10, and rostral 46, and finally through caudal areas 46 and 8. Within the basoventral sector gradual increases in the number of layers and their delineation are observed from the orbital PAll to the proisocortex, orbital area 25, area 13, then to orbital areas 12, 14, and 11, and then through ventrolateral areas 10, 12, rostral 46, and finally to caudal areas 46 and 8. Small dotted lines demarcate architectonic zones; large dotted lines demarcate sulci. Large numbers designate architectonic areas; small numbers refer to cases. In this and in subsequent maps showing the unfolded cortex the rostrocaudal dimension (right to left) was expanded by a factor of 2.5 (which accounts for differences in the shape of the injection sites between the maps shown in A–C and D). Triangles separate the dorsolateral from the medial surface (top) and the ventrolateral from the basal surface (bottom). Injection sites in mediodorsal prefrontal cortices are shown by the striped areas; in basoventral sites they are shown in black.

tures (Hilpert, '28; Brockhaus, '40; Humphrey, '68). We consider these facts to justify classification of APir as a separate anatomical entity distinct from VCo.

Based on the above considerations, there are five groups of nuclei in the monkey amygdala: olfactory, medial, central, basal, and intramedullary. On the basis of the hodological studies of Turner et al. ('78) describing the connectional relationship of the olfactory bulb and the amygdala in macaque monkeys, the olfactory amygdala consists of four nuclei [the nucleus of the lateral olfactory tract (LOT), the anterior (ACo), ventral (VCo), and posterior (PCo) divisions of the cortical nuclei] and two areas [the anterior amygdaloid (AAA) and the amygdalopiriform (APir)]. The nucleus of the lateral olfactory tract is small and not easily delineated in monkeys. The VCo nucleus has three subdivisions, which we refer to as the superior (S), the intermediate (It), and the inferior (If). The medial group in the monkey includes the medial (Me) nucleus and the amygdalohippocampal area (AHA). The central group consists only of the central nucleus (Ce) and the associated amygdaloid grisea. The basal group includes the basomedial (BM), basolateral (BL), and lateral (L) nuclei. Each of these three members of the basal group can be subdivided further into several subsectors (e.g., Amaral, '85; Price et al., '87). The fifth nuclear group of the amygdala comprises the intramedullary griseum. It is composed of small compact cell aggregates interposed between fiber bundles which form the medullary septa separating the different amygdaloid nuclei.

RESULTS

The location of the various amygdaloid nuclei and their gross architecture is shown in photomicrographs of Nissl coronal sections through the amygdala in Figure 1. Because the cytoarchitecture and various aspects of the chemoarchitecture of the amygdala have been described in other studies (e.g., Lauer, '45; Jimenez-Castellanos, '49; Mikami, '52; Price et al., '87; Amaral and Basset, '89), they will not be described here.

Retrograde tracer studies

Injection sites. The retrograde tracer injections were located in nine basoventral (HRP cases 1, 2, and 4–8 and FT case 3b, 3y), and seven mediodorsal (HRP cases 9, 10, 12, and 13 and FT cases 3r, 11y, and 11b) prefrontal regions (Fig. 2). The basoventral included six basal (orbital) sites (areas PAll and Pro, cases 1 and 2; area 13, case 3b; 012, cases 3y and 5; and area 11, case 4), and three ventrolateral sites below, or in the lower bank of the principal sulcus within ventral area 46 (cases 6–8). In one of the two area 12 cases, an injection of diamidino yellow was located in the caudal portion of orbital area 12 (case 3y); in the other an HRP injection was in the rostral portion of orbital area 12 (case 5). In the three ventral area 46 cases, HRP injections were located in the lower portion of area 46 (case 6), in a region just below the principal sulcus (case 7), and within the lower bank of the central extent of the principal sulcus (case 8). The mediodorsal prefrontal regions included five medial sites (area 25, case 9; area 32, cases 10, 3r and 11y; and area 14, case 11b) and two dorsolateral sites within area 8 (cases 12 and 13). In one of the three cases with retrograde tracers in area 32, an HRP injection covered its rostro-ventral portion (case 10), in another a diamidino yellow injection was within the central portion of area 32 (case 11y), and in a third a small injection of fluorescent latex microspheres was within the caudal portion of area 32 (case 3r). In case 3r traces from the dye injection were noted in the deep layers (V and VI) in proisocortical area 25. In both area 8 cases the HRP injection was in the caudal part of dorsal area 8. In all cases in this study the needle tracts were restricted to the cortical mantle, and there was no apparent damage to the underlying white matter.

Amygdaloid projections

Amygdaloid nuclei where labeled neurons were noted after HRP or fluorescent dye injections are shown in diagrams of cross sections in Figures 4–11. The distribution of labeled neurons in the various nuclei is shown in Table 1. Labeled neurons were noted in the BL, BM (also known as accessory basal), L, and in the VCo nuclei. A few labeled neurons were noted also in the amygdalopiriform (APir) and in the anterior amygdaloid (AAA) areas. Among the basoventral group, cases with injection in periallocortex or proisocortex (cases 1, 2) had the most labeled neurons of all cases studied. Cases with injections in regions situated immediately adjacent to the above (cases 3, 4) had fewer labeled neurons, and in a ventrolateral case (case 6) there were still fewer labeled neurons. In comparison to the above cases, labeled neurons were sparse after injection of retrograde tracers in a rostrolateral orbital area 12 site (case 5) or close to, or within, the lower bank of the principal sulcus (cases 7, 8). Among the mediodorsal group, cases with injection in ventromedial sites, such as in the lower portion of area 32 (case 10), area 25 (case 9), and area 14 (case 11b) had the most labeled neurons. However, as a group these cases had fewer labeled neurons than their architectonic counterparts in the caudal orbitofrontal region. Fluorescent dye injections in more dorsal and caudal portions of proisocortical area 32 (cases 3r, 11y), and HRP injection in dorsal area 8 (cases 12 and 13) resulted in only a few labeled neurons. Because the total number of labeled neurons from case to case varied greatly, both the proportion of labeled neurons in each nucleus and the total number of labeled neurons are shown in Table 1.

Basolateral (BL)

Most labeled neurons were noted in BL, and all cases studied had a substantial proportion of their labeled neurons in BL. However, the proportion of labeled neurons in BL directed to different prefrontal sites varied (Table 1). In the basoventral group, case 1 (with an injection of HRP primarily in the orbital periallocortex) had many more labeled neurons in the amygdala than the rest, and 26% of these (n = 548) were found in BL. Area 13, situated immediately rostral to the orbital proisocortex, had 51% of its labeled neurons (n = 300) in BL. The lateral portion of the orbital proisocortex (case 2) had 88% (n = 555), and area 11 situated rostral to area 13 had 89% (n = 370) of its labeled neurons in BL. In cases with injection of retrograde tracers in orbital area 12, or ventral area 46 (cases 3y, 5–8), all, or nearly all, (99%) of the labeled neurons were found in BL (Table 1).

In the mediodorsal group cases with injections in medial prefrontal sites had the lowest proportion of labeled neurons in BL (area 14 case 11b, 13%, n = 25; area 25 case 9, 30%, n = 39; and ventral area 32 case 10, 58%, n = 283); however, because these cases received more robust projections from the amygdala than the rest of the mediodorsal cases, the above percentages still constitute a substantial projection from BL (Table 1). In two other cases with

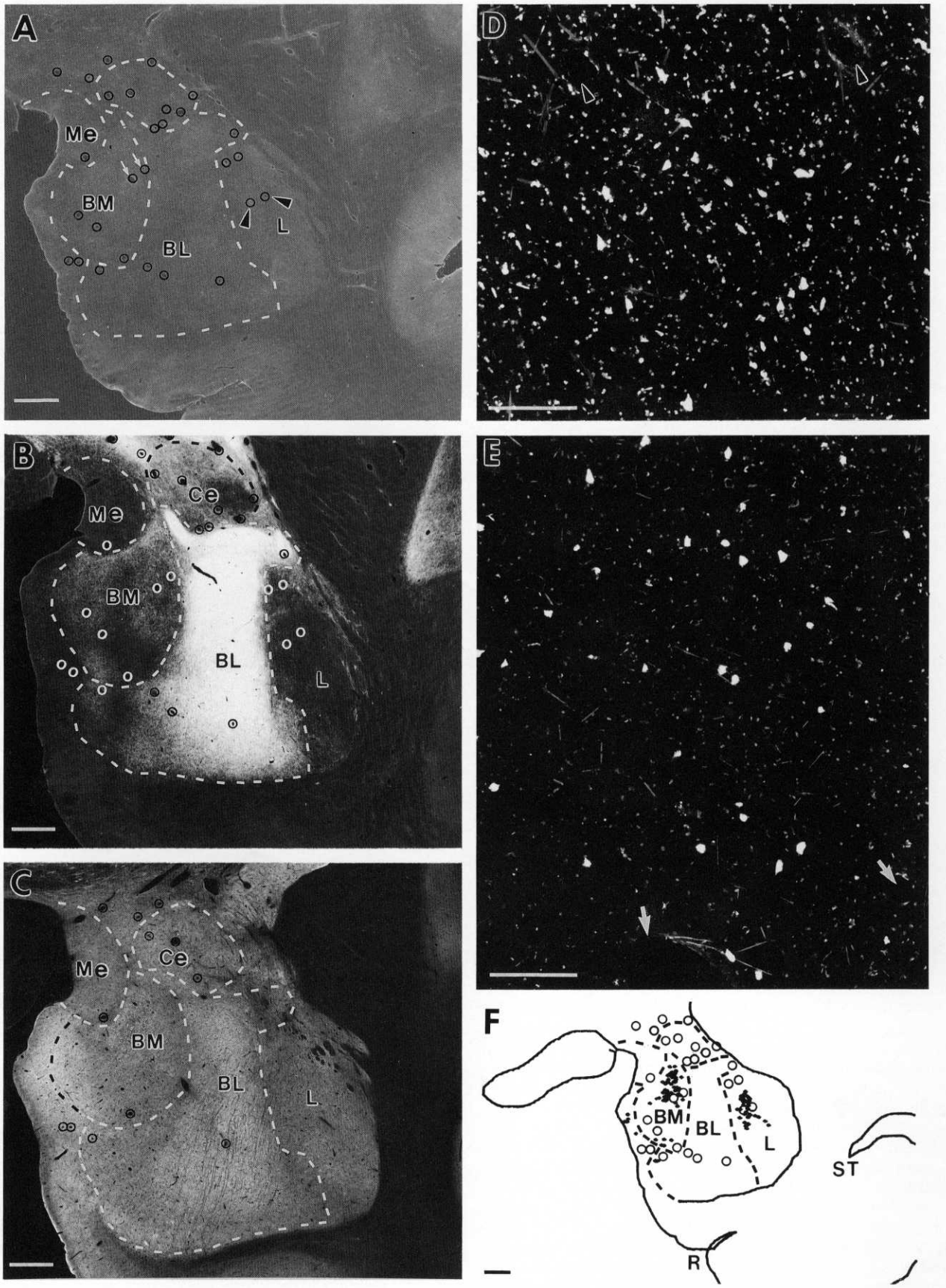

Figure 3

injection of fluorescent dyes in the more dorso-caudally situated portions of area 32, 75% (case 3r, n = 15) and 83% (case 11y, n = 15) of all labeled neurons were found in BL. In the dorsolateral area 8 cases (case 12, n = 19 and case 13, n = 16) all labeled neurons were found in BL.

Location of labeled cells within BL. *Dorso-ventral.* Labeled neurons were found throughout the dorsoventral extent of BL but there were variations in the specific sites of label from case to case. Among the basoventral group, in cases with injections in orbital periallocortex, proisocortex, area 13, and orbital area 12 (cases 1, 2, 3b, 3y), there was a higher proportion of labeled neurons in the two ventral sectors of BL when compared with the rest of the cases (Figs. 4–6, 12A). In cases with injections in area 11 and the most ventral portion of area 46 the majority of labeled neurons were found in the central sectors of BL (Figs. 7, 8A–C, 12B). In cases with HRP injections in area 46 just below or within the lower limb of the principal sulcus (cases 7, 8), most labeled neurons were found in the two dorsal sectors of BL (Figs. 8D–F, 12C). An example of the distribution of labeled neurons in each of the above categories is shown in a histogram in Figure 12.

Among the mediodorsal group labeled neurons were found primarily in the central sectors of BL in cases with injection of tracers in areas 25, 32, and 14 (cases 9; 10; 3r, 11y and 11b, Figs. 9, 10). Because the distribution of labeled neurons within the dorso-ventral extent of BL in these cases was similar, the data were pooled and are shown in Figure 13A. In contrast, in the two cases with HRP injection in area 8, labeled neurons were found only in the two dorsal sectors of BL (Figs. 11, 13B).

Medio-lateral. There were no major differences in the medio-lateral position of labeled neurons within BL among the basoventral, or among the mediodorsal cases. However, there were differences between the two groups of cases. The basoventral cases had most of their labeled neurons in the central parts of BL and fewer in its lateral and medial sectors (Figs. 4–8, 14A). In the mediodorsal cases most labeled neurons were found in more lateral parts of BL and none in its most medial sector (Figs. 9–11, 14B).

Rostro-caudal. Labeled neurons were found at all rostro-caudal levels of the BL nucleus. Even though there was considerable overlap, as a group the orbital cases (cases 1, 2, 3b, 4, 3y, and 5) had more labeled neurons in the caudal sectors of BL (Figs. 4–6, 15A) when compared with the ventrolateral (cases 6–8; Figs. 8, 15B). In cases with medial injections (9, 10, 11y, 3r, and 11b) labeled neurons were found in the caudal 4 of the 5 BL sectors (Figs. 6, 9, 10, 15C). Labeled neurons directed to dorsal area 8 were concentrated in the central extent of BL (Figs. 11, 15D).

Basomedial (BM)

In most cases labeled neurons were noted in the BM nucleus. In the basoventral group, most labeled neurons in BM were found in cases with HRP injection in area PAll (case 1, 29%, n = 617; Fig. 4) or a fast blue injection in area 13 (case 3b, 39%, n = 231; Fig. 6). Cases with HRP injection in the adjacent orbital proisocortex and area 11 also had some labeled neurons in BM (case 2, 10%, n = 66; case 4, 11%, n = 47; Figs. 5, 7). In cases with more lateral injections, such as in area 12 (case 3y; Fig. 6) or the adjacent portion of ventral area 46 (case 6; Fig. 8), only a few (1%) of the labeled neurons were found in BM. There was no evidence of labeled neurons in BM in cases with HRP injection in area 46 within the lower bank of the principal sulcus or in its subjacent sector (cases 7 and 8).

All of the cases with injection of retrograde tracers in medial prefrontal areas had some labeled neurons in the BM nucleus. Of these, cases with medial injections situated below the level of the corpus callosum had the highest proportion of their labeled neurons in BM (case 11b, 87%, n = 163; Fig. 10; case 9, 67%, n = 87; Fig. 9A–D; and case 10, 40%, n = 197; Fig. 9E–H). In cases with fluorescent dye injections in more central and caudal sectors of area 32 the proportion of labeled neurons in BM was lower (case 3r, 15%; 11y, 17%; Figs. 6, 10). There was no evidence of labeled neurons in BM in cases with HRP injection in area 8.

Location of labeled neurons within BM. *Dorso-ventral.* In basoventral cases 1, 2, and 3b, which had a significant number of labeled neurons in BM, the labeled neurons were scattered throughout the dorso-ventral extent of the nucleus (Figs. 4, 5, 6b). In contrast, labeled neurons directed to the more rostrally situated orbital area 11 were concentrated in the dorsal parts of BM (Fig. 7). In the mediodorsal cases, most labeled neurons were clustered in the central and dorsal sectors of BM (Figs. 6r, 9, 10).

Medio-lateral. There were no major differences among basoventral cases with respect to the medio-lateral position of labeled neurons, or among mediodorsal cases, and only slight differences were observed between these two groups of cases. Most labeled neurons were found in the central sector of BM in the basoventral cases (Figs. 4–6), whereas in the mediodorsal cases labeled neurons were found somewhat more laterally (Figs. 9, 10).

Rostro-caudal. In cases with HRP injection in caudal orbitofrontal regions, labeled neurons were found in all rostro-caudal levels of BM (cases 1, 2, 3b; Figs. 4–6). In contrast, in cases with injection of retrograde tracers in area 11 (Fig. 7) or the orbital portion of caudal area 12 (case 3y; Fig. 6y) labeled neurons were found only in the caudal sectors of BM. In the mediodorsal cases most labeled neurons were found in the central (case 9, Fig. 9A–D) or caudal (case 10, Fig. 9E–H) sectors of BM.

Lateral (L)

Labeled neurons in the lateral amygdaloid nucleus were found in significant numbers only in case 1 with HRP injection in orbital PAll (40%, n = 855; Fig. 4). A few labeled neurons in L were seen also in cases with an injection of fast blue in area 13 (case 3b, 3%; Fig. 6) or HRP in orbital proisocortex (case 2, <1%; Fig. 5) but not in any

Fig. 3. Photomicrograph of a coronal section through the amygdala of tissue reacted for the visualization of HRP (**A**), and matched sections reacted for the enzymes AChE (**B**) and cytochrome oxidase (**C**). These photographs were obtained by direct projection of mounted histological tissue onto photographic paper. White areas and grains in B and C show enzymatic activity. Labeled neurons in the lateral nucleus are seen in a darkfield photomicrograph at higher magnification in **D**, and in the basomedial nucleus in **E**. **F** shows the entire distribution of labeled neurons in the amygdala (black dots) in a charting of the section depicted in A using the computerized system for data analysis described in Methods. Circles in A, B, C, and F overly common blood vessels used as landmarks to aid in delineating architectonic borders. Arrows in A, D, and E show regions within the lateral nucleus (silhouette arrowheads) and in the basomedial nucleus (solid white arrows) that contain labeled neurons. Scale bar is 1 mm for A, B, C, and F and 100 μm for D and E.

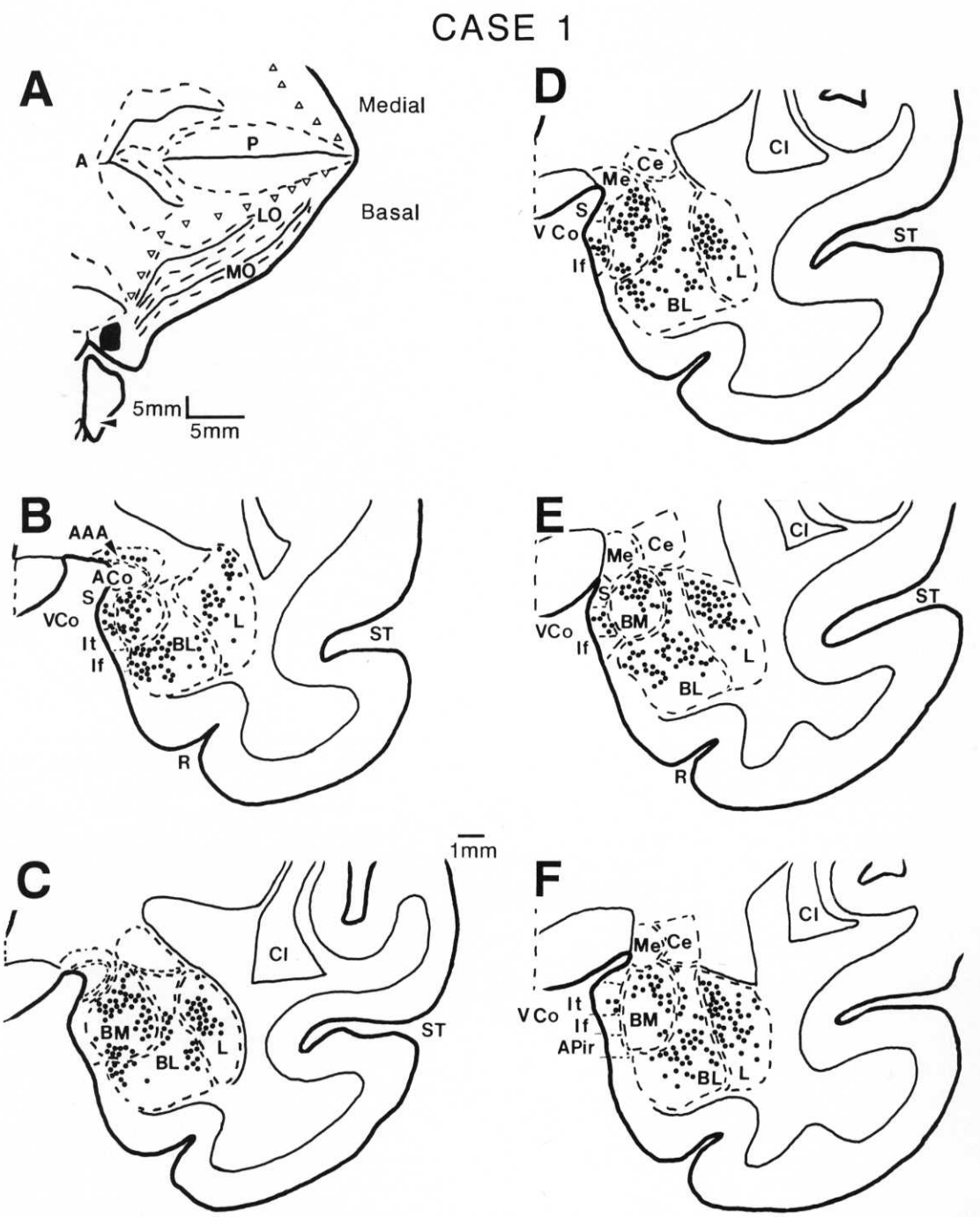

Fig. 4. The distribution of labeled neurons in the amygdala (represented by dots in coronal sections **B–F**) in case 1 after HRP injection (black area) in orbital periallocortex and, to a lesser extent, proisocortex (**A**). The injection site in this and in most other cases is shown on a map where the prefrontal cortex was unfolded (A). Open triangles in this and in all other figures separate the dorsolateral from the medial surface (top) and the ventrolateral from the basal surface (bottom); dots indicate labeled neurons. The arrowhead (A) points to the temporal pole.

of the other basoventral cases. Most labeled neurons in L were found in the dorso-medial sectors of the nucleus and were concentrated caudally (Figs. 4, 6). There was no significant labeling in the lateral nucleus after injection of retrograde tracers in mediodorsal, or the rest of the prefrontal sites studied.

Ventral cortical (VCo)

A few labeled neurons were found in the VCo nucleus after HRP injection in orbital PAll (case 1, 4%, n = 85; Fig. 4), the adjacent area 13 (case 3b, 3%, n = 18; Fig. 6), and orbital proisocortex (case 2, 1%; Fig. 5). Mediodorsal cases

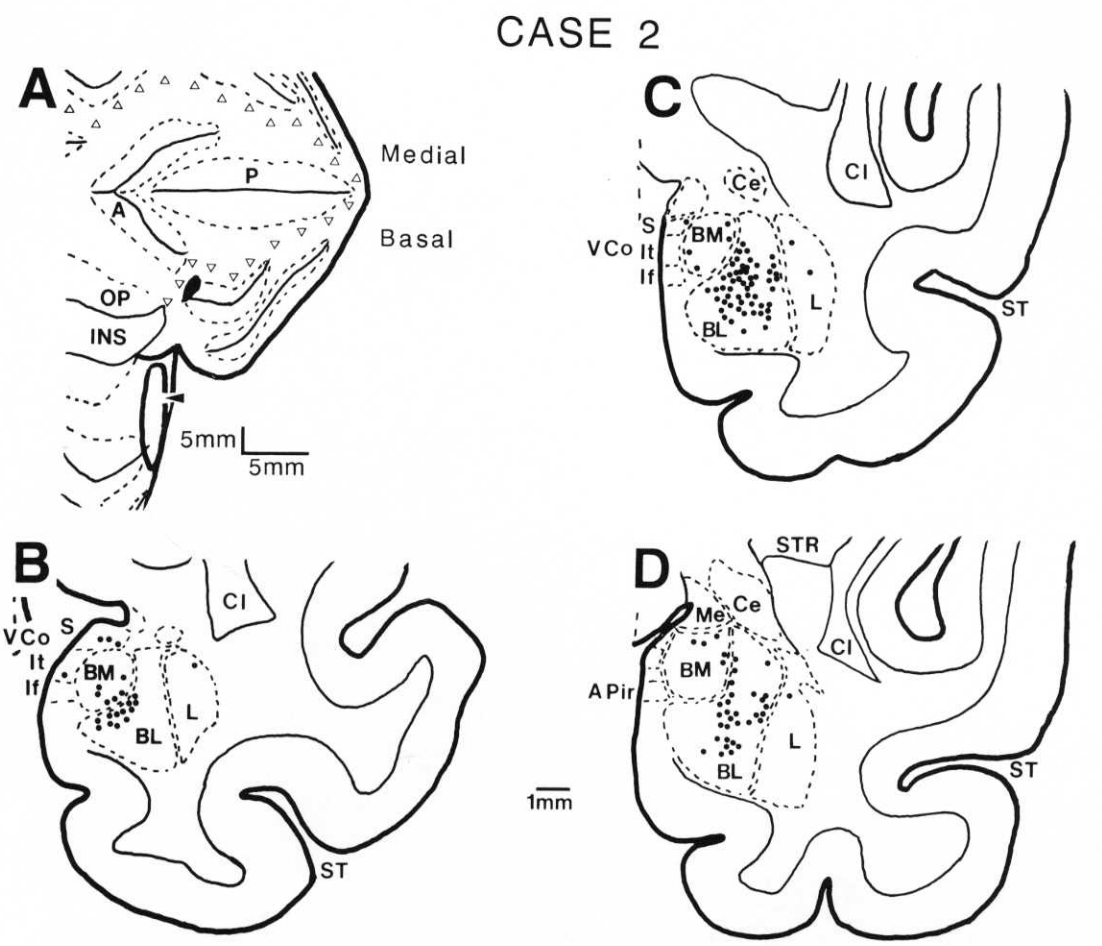

Fig. 5. The distribution of labeled neurons in the amygdala (**B–D**) in case 2 after an HRP injection in the orbital proisocortex (**A**). The arrowhead in A points to the temporal pole.

with HRP injection in area 25 or the rostral portion of area 32 also had a few labeled neurons in the VCo nucleus (case 9, 2%; Fig. 9D; case 10, 1%). Most of the labeled neurons in the VCo were found in its superior and intermediate subdivisions, and very few were noted in its inferior sector.

Anterior amygdaloid area (AAA)

Only a few labeled neurons were found in the above area after HRP injection in orbital PAll (case 1, $<0.5\%$; Fig. 4B) or in the rostral part of area 32 (case 10, $<0.5\%$; Table 1).

Amygdalopiriform area (APir)

A few labeled neurons were found in the amygdalopiriform area, mostly after injection of fast blue in area 13 (case 3b, 4%, n = 25; Fig. 6C,D), the orbital periallocortex (case 1, $<1\%$), and the caudal part of area 32 (case 3r, 10%; Fig. 6F).

DISCUSSION

The present findings indicate that there are widespread projections from the amygdala to the prefrontal cortex in the rhesus monkey. Prefrontally directed amygdaloid neurons are found in large numbers in the basolateral and basomedial nuclei, but also in subareas of the cortical, and lateral nuclei, and the amygdalopiriform and anterior amygdaloid areas. These data confirm and extend previous findings (Nauta, '61; Potter and Nauta, '79; Pandya et al., '73; Jacobson and Trojanowski, '75; Porrino et al., '81; Price, '81; Amaral and Price, '84; Amaral, '85).

The prefrontal areas described in this study represent sites within two sectors in the prefrontal cortex (Barbas and Pandya, '89). These sectors were identified using architectonic and connectional criteria and have been referred to as basoventral and mediodorsal on the basis of their anatomic location. Each sector is composed of regions which have different degrees of laminar organization. Within the basoventral sector the least architectonically differentiated areas are found in the caudal orbitofrontal region. These limbic areas are characterized by an incipient laminar organization where three or fewer layers can be identified. Stepwise increases in laminar organization are observed in a radial direction towards more rostral orbital and then ventrolateral areas towards the lower limb of the arcuate sulcus. Within the mediodorsal group the least differentiated areas include the periallocortex and proisocortical areas 24, 25, and 32, situated around the rostral tip of the corpus

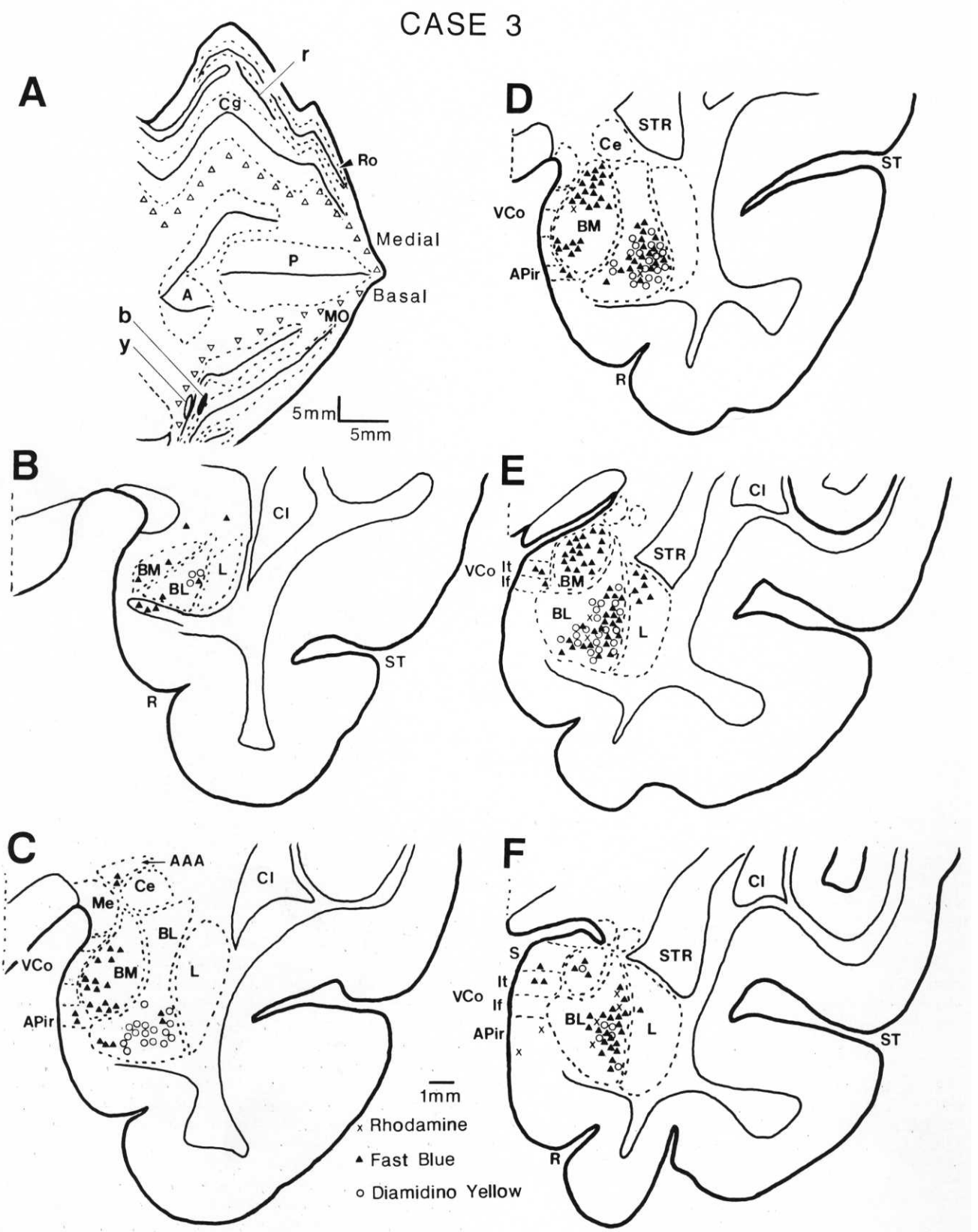

Fig. 6. The distribution of labeled neurons in the amygdala (**B–F**) in case 3 after injection of three fluorescent dyes (**A**): fast blue in area 13 (b, in A, case 3b); diamidino yellow in orbital area 12 (y in A, case 3y); and rhodamine-labeled microspheres in caudal area 32 (r in A, case 3r).

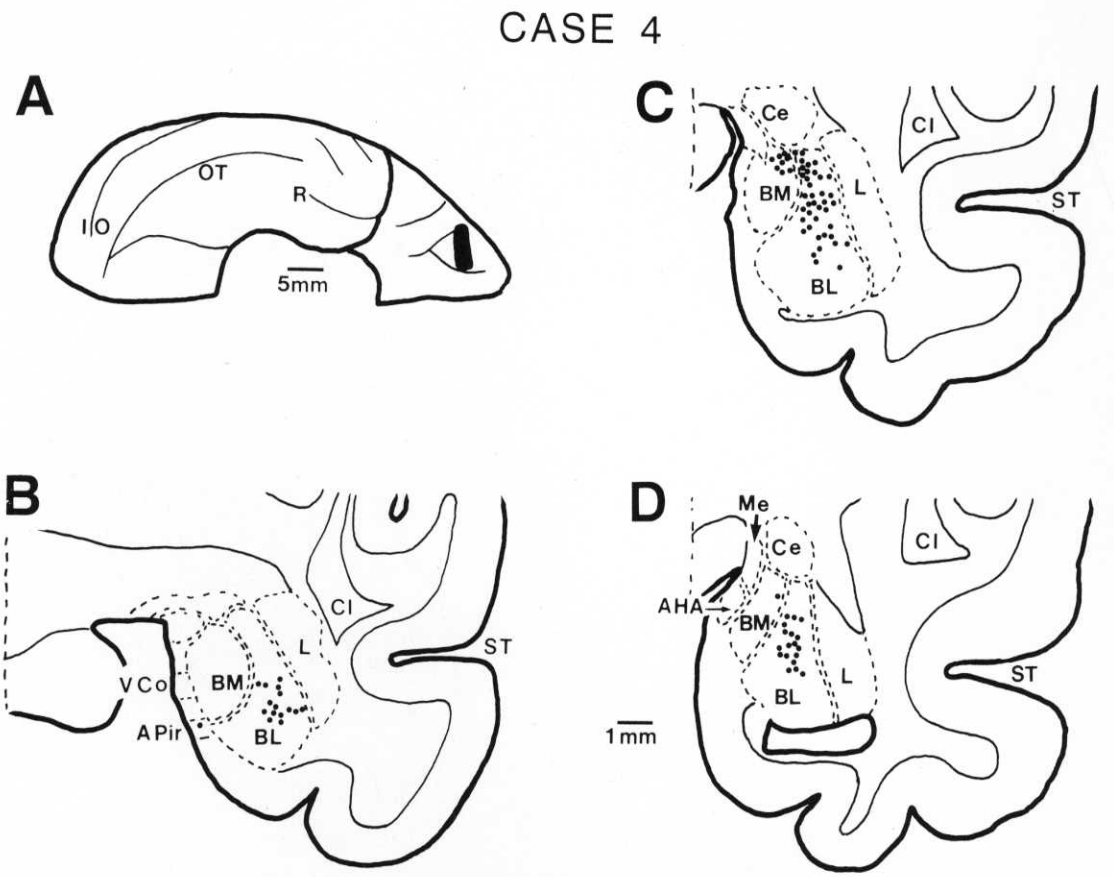

Fig. 7. The distribution of labeled neurons in the amygdala (**B–D**) in case 4 after HRP injection in area 11 (**A**).

callosum. Gradual increases in the number of layers and their delineation are observed first in adjacent rostromedial and then dorsolateral areas towards the upper limb of the arcuate sulcus. Areas 46 and 8 represent the last stage in this architectonic progression and exhibit the highest degree of laminar organization within the prefrontal cortex.

The question addressed here is whether there are differences in the origin of amygdaloid projections directed to sites within the basoventral or mediodorsal sectors. Because the limbic cortices and their immediate neighboring areas are the major targets of amygdaloid projections, they will be discussed first. The data presented indicate that the caudal orbitofrontal limbic areas (cases 1, 2, and 3b) receive more projections from amygdaloid nuclei than the medial limbic cortices (areas 25 and 32). There are also qualitative differences in the amygdaloid projections directed to these two cortical groups. For example, the BM nucleus projects to both orbital and medial cortices; however, it provides a higher proportion of all projections directed to the lower parts of the medial cortices (cases 9, 10, and 11b) than to basal cortices. In addition, the orbital periallocortex and, to a lesser extent, adjacent areas receive projections from the lateral amygdaloid nucleus. In contrast, medial limbic sites have few, if any, links with the lateral nucleus.

The topography of projections from one amygdaloid nucleus directed to basoventral versus mediodorsal prefrontal sites differs as well. For example, labeled neurons in BL projecting to basoventral prefrontal cortices are more centrally located within the medio-lateral extent of the nucleus and more ventrally located within its dorso-ventral extent when compared to the origin of projections directed to mediodorsal prefrontal sites. The same tendency was observed for projections from BM, albeit not as clearly.

In addition to the general differences in the origin of amygdaloid projections directed to basoventral versus mediodorsal cortices, there are differences in the connectional organization of areas within a group of cortices. For example, the orbitofrontal cortices are the least differentiated within the basoventral sector and have the strongest and topographically the most diverse links with the amygdala. In contrast, ventrolateral cortices within or below the lower bank of the principal sulcus (ventral area 46), which have better-delineated layers, receive fewer amygdaloid projections. Moreover, these projections originate from topographically restricted amygdaloid loci. Within the mediodorsal group of cortices, the most robust and topographically varied amygdaloid projections are directed to those limbic proisocortices and the adjacent area 14 situated rostrally and ventrally on the medial surface of the hemisphere. The more caudal and dorsal proisocortices, as well as isocortical area 8, receive only a few projections from the amygdala. Moreover, even though caudal and central proisocortical area 32 (cases 3r, 11y) and dorsal area 8 (cases 12, 13) receive equally sparse projections, those directed to the eulaminated area 8 are also topographically restricted (Table 1). The above evidence suggests that influences from widespread amygdaloid nuclei are exerted primarily on the caudal orbital, followed by the ventrome-

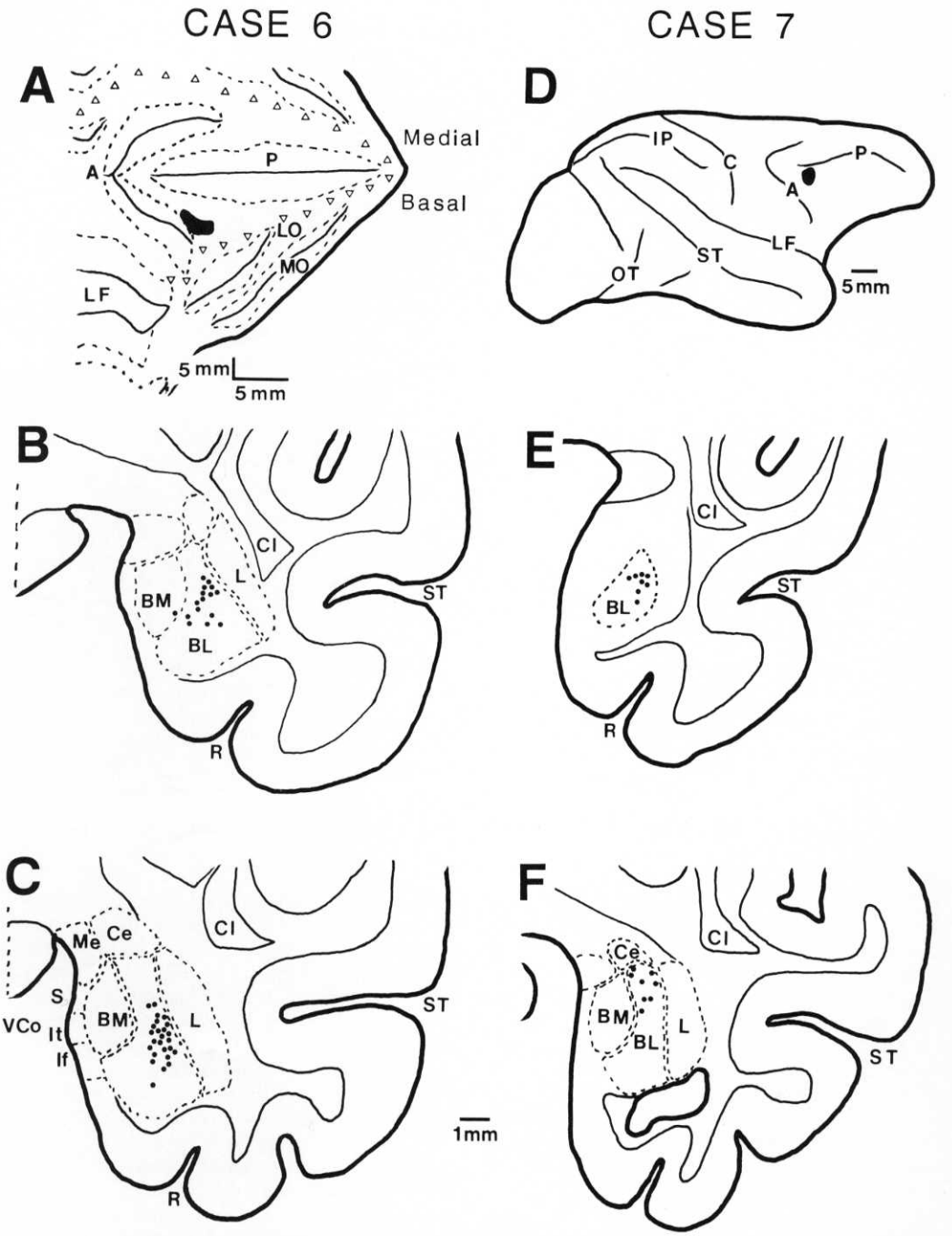

Fig. 8. The distribution of labeled neurons in the amygdala after HRP injection in the lower portion of ventral area 46 (case 6, **A**) is shown in **B–C;** and after HRP injection in ventral area 46 just below the caudal part of the principal sulcus (case 7, **D**) is shown in **E–F.**

dial prefrontal cortices. These amygdaloid projections originate from all components of the basal complex, as well as from the ventral cortical, anterior amygdaloid, and amygdalopiriform areas from the olfactory amygdala. In contrast, the most differentiated cortices within both prefrontal sectors receive fewer and topographically restricted amygdaloid projections. The BL nucleus seems to be the exclusive source of projections to the most architectonically differentiated prefrontal cortices.

There were also topographic differences in the origin of amygdaloid neurons projecting to different loci within the basoventral or the mediodorsal cortices. For example, labeled neurons in the BL nucleus directed to those basoventral or mediodorsal cortices characterized by a low degree of laminar organization were scattered throughout the rostrocaudal extent of the nucleus, with substantial numbers found in its caudal sectors. In contrast, there were fewer labeled neurons in the caudal parts of BL projecting to

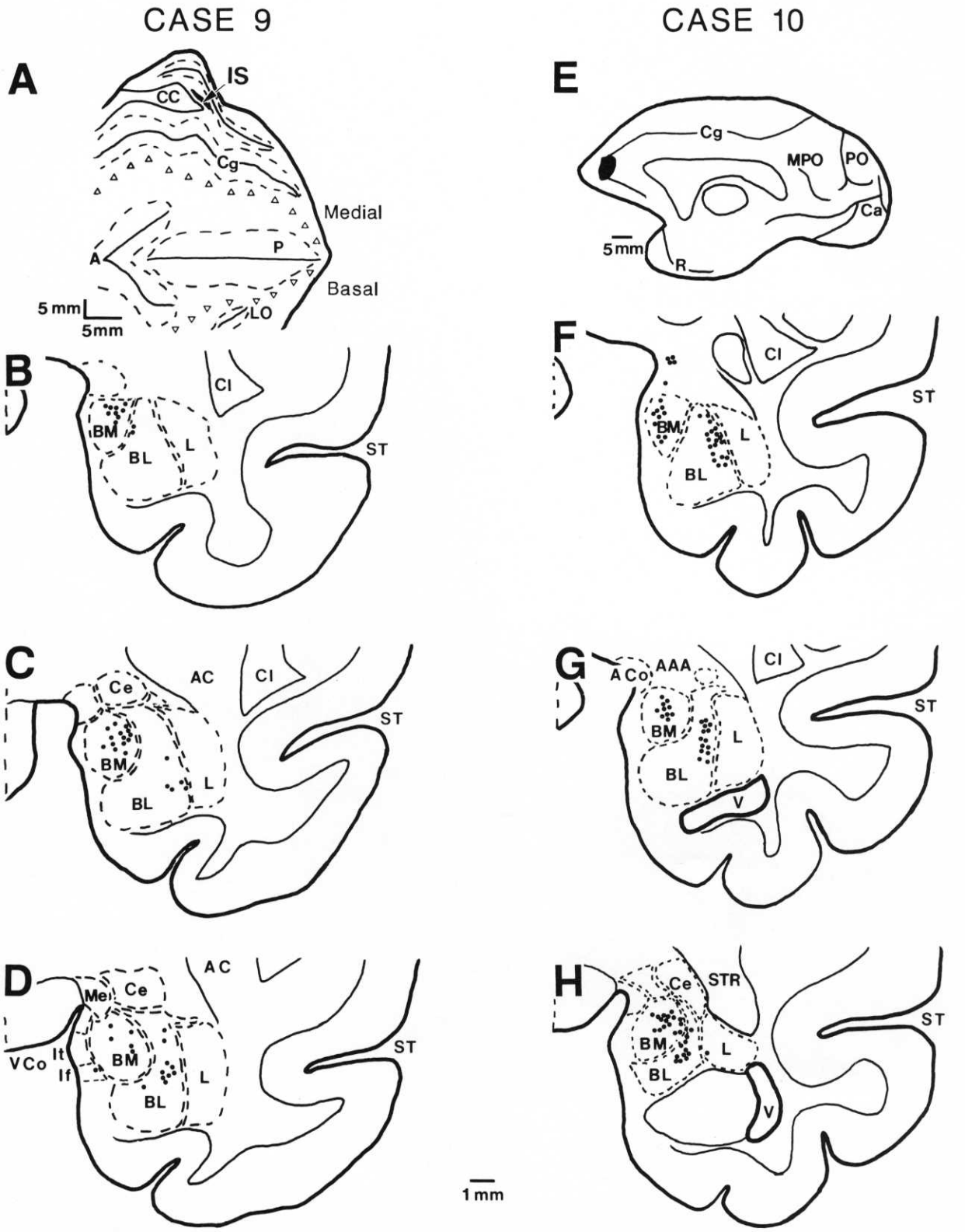

Fig. 9. The distribution of labeled neurons in the amygdala in case 9 after HRP injection in area 25 (**A**) is shown in **B–D,** and in case 10 after HRP injection in the rostral part of area 32 (**E**) is shown in **F–H.**

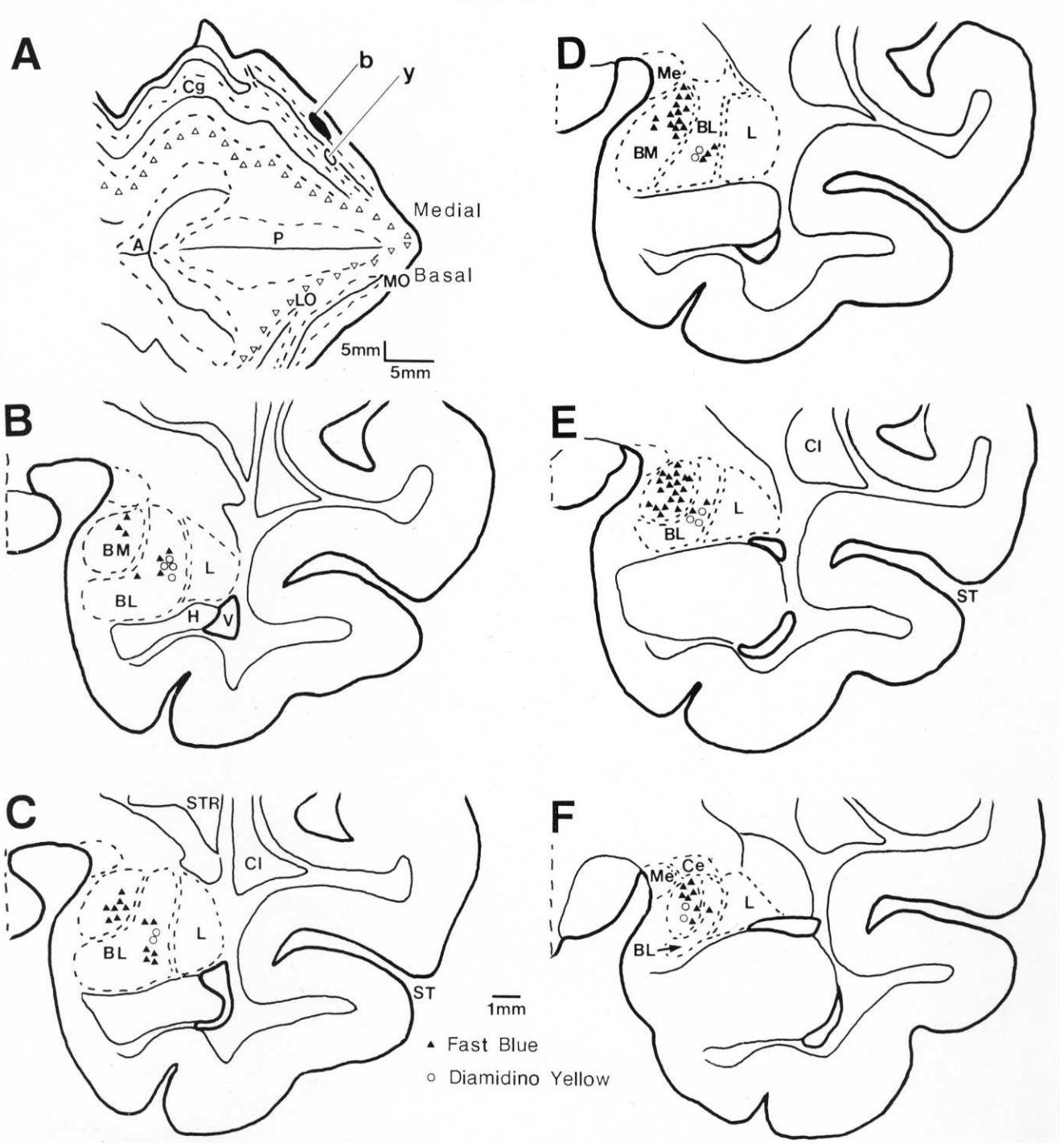

Fig. 10. The distribution of labeled neurons in the amygdala (**B–F**) in case 11 after injection of two fluorescent dyes (**A**): fast blue in area 14 (b, in A, case 11b) and diamidino yellow in central area 32 (y, in A, case 11y).

areas with better delineated layers. Moreover, neurons in BL projecting to caudal orbital areas were concentrated ventrally. There was a shift in the location of labeled neurons to more central and dorsal sectors of BL in cases with injection of retrograde tracers in increasingly more rostral orbital and ventrolateral cortices (Fig. 12). Similarly, labeled neurons directed to medial prefrontal cortices were found in substantial numbers in the central part of BL, whereas neurons projecting to dorsal area 8 were found in more dorsal sectors of the nucleus (Fig. 13).

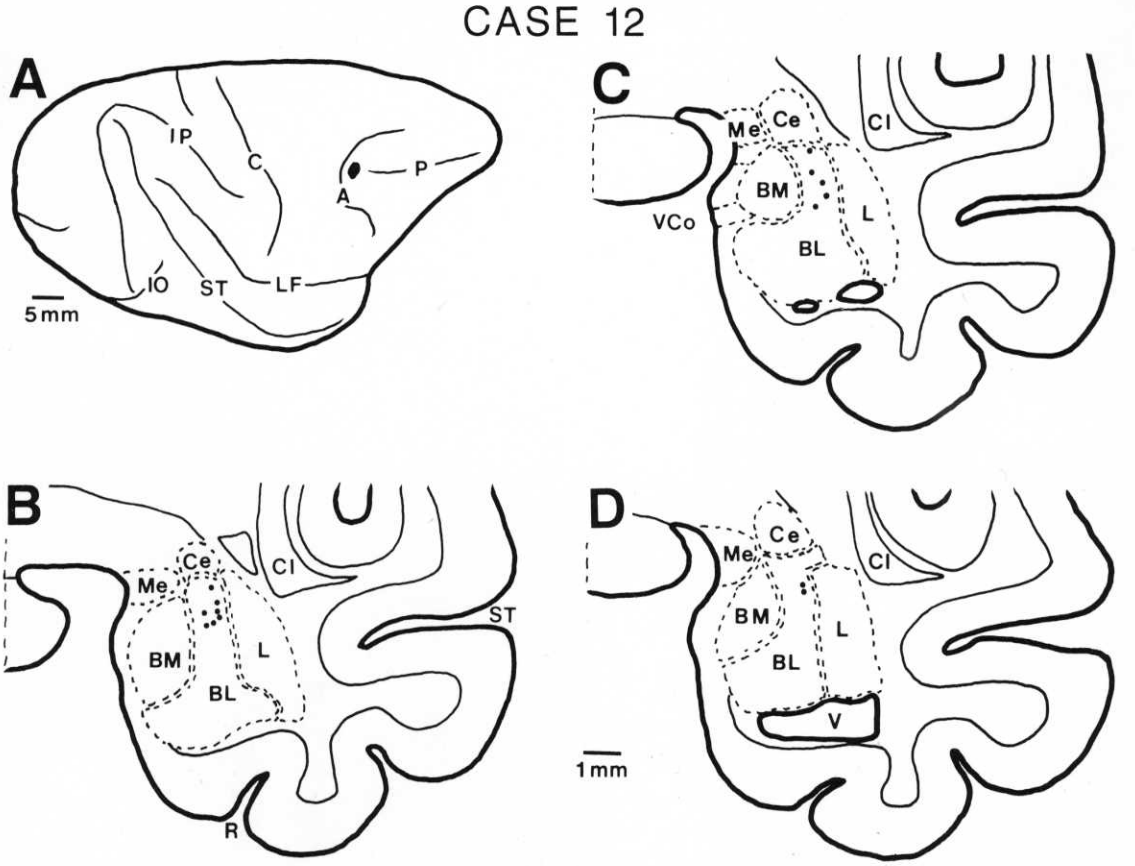

Fig. 11. The distribution of labeled neurons in the amygdala (**B–D**) in case 12 after injection of HRP in dorsal area 8 (**A**).

TABLE 1. Distribution of Labeled Neurons in the Amygdala After Injection of Retrograde Tracers in Basoventral and Mediodorsal Prefrontal Regions[1]

		Amygdaloid projection zone						
Case	Injection site	VCo	AAA	APir	BM	BL	L	Total N
Basoventral								
1	PAll-Pro	4	<0.5	<1	29	26	40	2,130
2	Pro	1	—	—	10	88	<1	633
3b	13	3	—	4	39	51	3	588
4	11	—	—	<0.5	11	89	—	418
3y	012	—	—	—	1	99	—	257
5	012	—	—	—	—	100	—	11
6	46	—	—	—	<1	99	—	239
7	46	—	—	—	—	100	—	85
8	s46	—	—	—	—	100	—	3
Mediodorsal								
9	25	2	—	—	67	30	<1	129
10	32	1	<0.5	—	40	58	<0.5	489
3r	32	—	—	10	15	75	—	20
11y	32	—	—	—	17	83	—	18
11b	14	—	—	—	87	13	—	188
12	8	—	—	—	—	100	—	19
13	8	—	—	—	—	100	—	16

[1]Data in columns below nuclear designations are expressed in percentages. The last column (total N) shows the total number of labeled neurons in the amygdala in each case. Abbreviations here and throughout the Tables are as in list preceding Figure 1.

Architectonic trends similar to the prefrontal have been described for other cortical systems as well (Pandya et al., '88 for review). A general finding is that laminar organization on the dorsolateral convexity of the cerebral cortex in monkeys decreases consistently with distance from the primary areas (Sanides, '70, '72; Pandya and Seltzer, '82; Galaburda and Pandya, '83; Rosene and Pandya, '83). When examined in the context of cortical architecture, patterns consistent with those we report here emerge. For example, in monkeys there are projections from the amygdala to the premotor but not to the motor cortex (Avendano et al., '83). The latter shows the highest degree of laminar organization within the cortical motor system (Barbas and Pandya, '87). Similarly, amygdaloid efferent fibers terminate preferentially in the less architectonically differentiated agranular part of the insula, and to a lesser

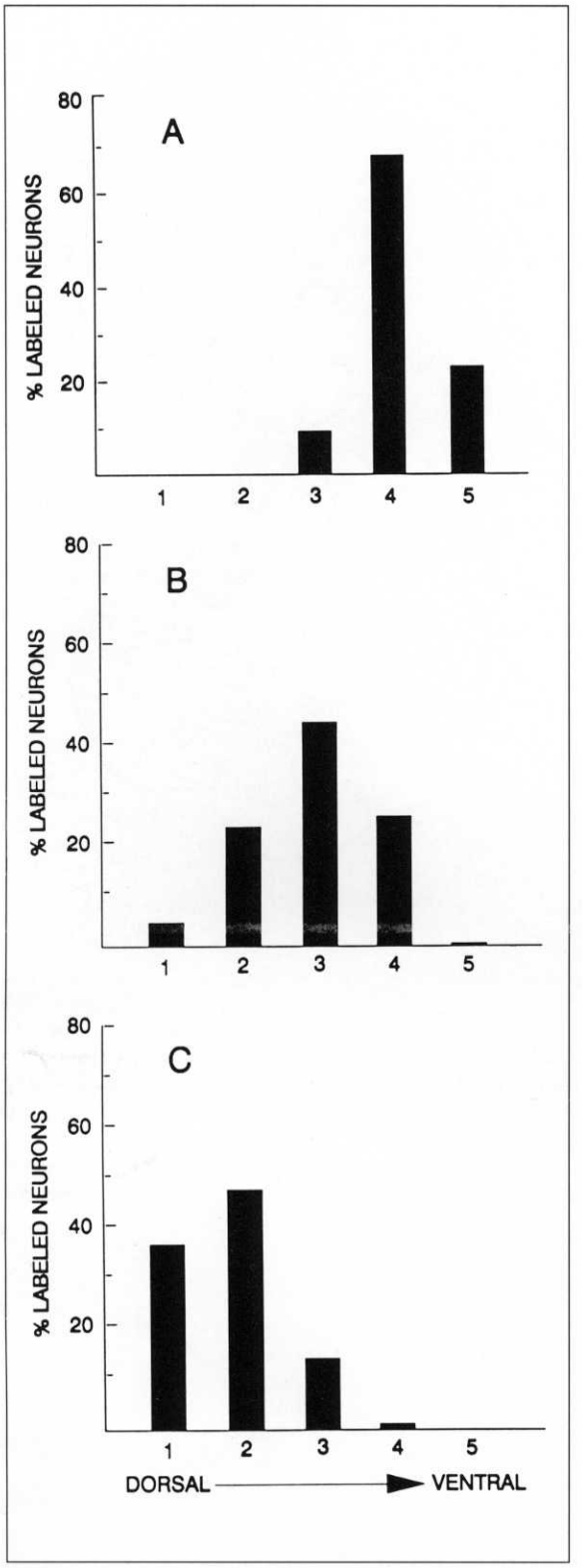

Fig. 12. Histograms showing the distribution of labeled neurons within the dorsal (shown in category 1) and in progressively more ventral sectors of the BL nucleus (5) in three basoventral prefrontal regions: **A:** case 3b, fast blue injection in orbital area 13; **B:** case 4, HRP injection in area 11; and **C:** case 7, HRP injection in ventral area 46.

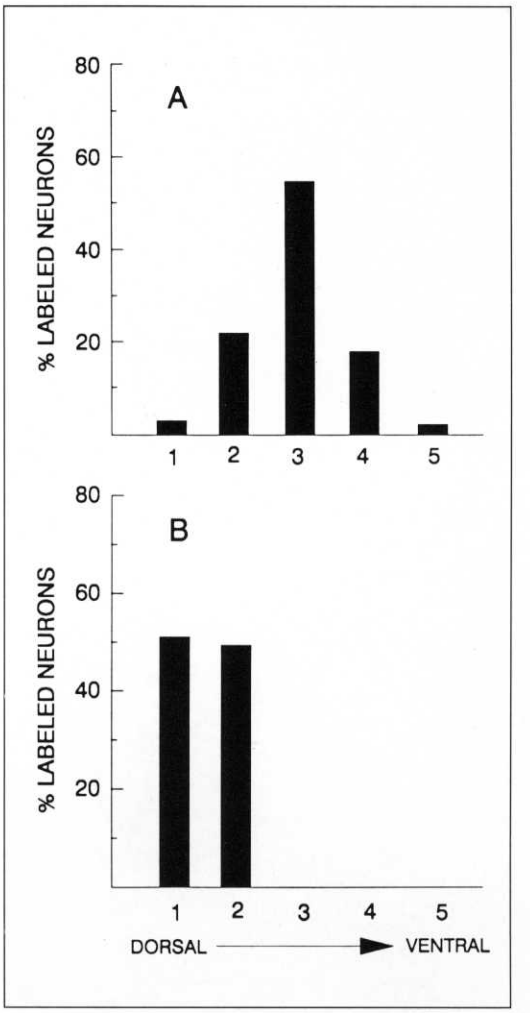

Fig. 13. Histograms showing the distribution of labeled neurons within the dorsal (shown in category 1), and in progressively more ventral (5) sectors of the BL nucleus in cases with injections of retrograde tracers in medial prefrontal cortices (**A,** cases 9, 10, 3r, 11y, 11b) and in dorsolateral prefrontal cortices (**B,** cases 12 and 13).

extent in the more architectonically differentiated dysgranular and granular portions of the insula (Amaral and Price, '84). Amygdaloid efferent fibers also terminate more robustly in the anterior and less differentiated auditory areas than in its more caudal sectors (Amaral and Price, '84), which have better delineated layers (Galaburda and Pandya, '83). The reciprocal efferent projections from the visual and auditory cortical systems that terminate in the amygdala show a similar pattern. Thus, anterior area TE sends a heavier projection to the amygdala than posterior area TE, which has better delineated layers, as do anterior versus posterior sectors of the auditory cortices (Whitlock and Nauta, '56; Turner et al., '80; Iwai and Yukie, '87). Taken together this evidence suggests a parallel between cortical laminar organization and preponderance of connections with amygdaloid areas. Amygdaloid connections thus seem to be richer with cortices that have a less-well differentiated laminar organization in all systems hitherto studied.

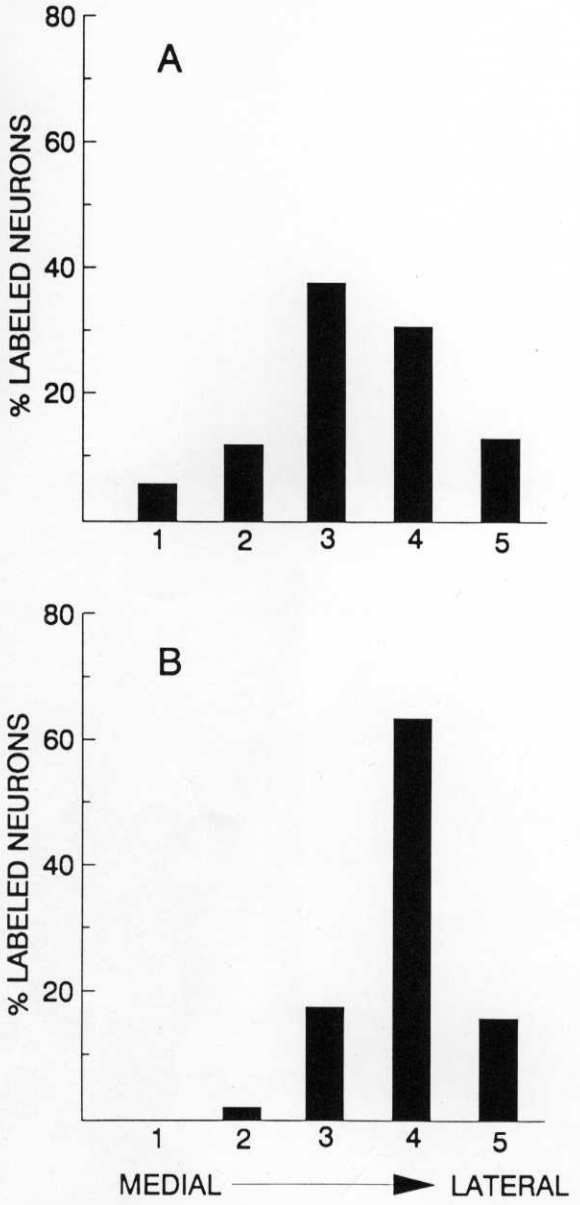

Fig. 14. Histograms showing the distribution of labeled neurons within the medial (shown in category 1) and in progressively more lateral (5) sectors of the BL nucleus after HRP injection in basoventral (**A**) and mediodorsal (**B**) prefrontal sites.

The nature of signals directed from the amygdala to the prefrontal cortex is not known. However, there is information on the type of projections reaching amygdaloid sites which, in turn, project to specific prefrontal areas. For example, input from visual cortices reaches primarily the antero-dorsal parts of the lateral and basolateral nuclei (Herzog and Van Hoesen, '76; Turner et al., '80; Van Hoesen, '81). Auditory projections terminate generally in the caudal sectors of the lateral, basolateral, and basomedial (accessory basal) nuclei (Turner et al., '80). The orbital and medial limbic prefrontal cortices, as shown in this study, receive projections from amygdaloid sites that receive input from the visual and, to a larger extent, from the auditory cortices. Insular projections, which probably convey somatosensory signals, are directed to the dorsal parts of the lateral, the anterior amygdaloid area, the cortical, and the basomedial (accessory basal) nuclei (Mufson et al., '81; Friedman et al., '86). These amygdaloid nuclei project only to the orbital and ventromedial limbic prefrontal cortices, as shown in this study. Olfactory signals may also reach the orbital and medial limbic prefrontal cortices via the cortical amygdaloid nuclei (Turner et al., '80; Tanabe et al., '75). Taste afferents are directed to the medial part of the lateral amygdaloid nucleus (Turner et al., '80; Van Hoesen, '81), which, in turn, projects to the orbital periallocortex and, to a lesser extent, the proisocortex. In addition, cortical amygdaloid areas and the boundaries of BL, which are active during ingestion of food (Nishijo et al., '88a;b), overlap with areas that send robust projections to the orbital and medial limbic prefrontal cortices. This evidence suggests that the least architectonically differentiated orbital and medial prefrontal cortices receive projections from amygdaloid loci that are targets of several sensory modalities. In contrast, the most differentiated prefrontal cortices (caudal areas 46 and 8) receive projections from the dorsal part of the BL nucleus, where neurons respond to visual stimuli (Nishijo et al., '88a) and are connected primarily with visual cortices (Herzog and Van Hoesen, '76; Van Hoesen, '81; Iwai and Yukie, '87; Iwai et al., '87).

In recent studies we showed that the limbic prefrontal cortices on the orbital and medial surfaces have widespread cortical connections originating in several sensory cortical systems (Barbas, 1988a,b). Similarly, the amygdaloid sites that project to these limbic prefrontal cortices are themselves targets of the same sensory modalities. In contrast, areas with a high degree of laminar organization have restricted cortical connections with areas associated with one or two sensory modalities. One of these zones, area 8, receives the majority of its cortical projections from visual and visuomotor areas (Barbas and Mesulam, '81; Barbas, '88b), and its amygdaloid projections originate in the dorsal part of BL, an area that seems to be a major target of the visual cortices as well (Turner et al., '80; Herzog and Van Hoesen, '76; Van Hoesen, '81; Iwai and Yukie, '87). The above data suggest that the qualitative nature of signals from amygdaloid nuclei to the prefrontal cortex parallels those transmitted via cortical pathways to the same prefrontal cortices.

Previous investigators have suggested that neocortical structures project more laterally within the amygdala, and older cortical structures such as the temporal pole and the perirhinal region project more medially (Herzog and Van Hoesen, '76), a pattern that parallels the ontogenetic development of the amygdala (Humphrey, '68). Our data are partially consistent with that view, in that the most medially situated amygdaloid structures, including the cortical and the basomedial, have a connectional relationship with the limbic prefrontal cortices. However, parts of the lateral nucleus also have strong links with the limbic periallocortex and, to a lesser extent, the proisocortices on the orbital surface. In contrast, the most differentiated prefrontal areas receive projections only from the dorsal portion of the BL nucleus. Similarly, previous investigators have shown that the lateral and accessory basal (our BM) nuclei project to the entorhinal cortex, a periallocortical region. The BL nucleus, on the other hand, projects to the slightly more architectonically differentiated (proisocorti-

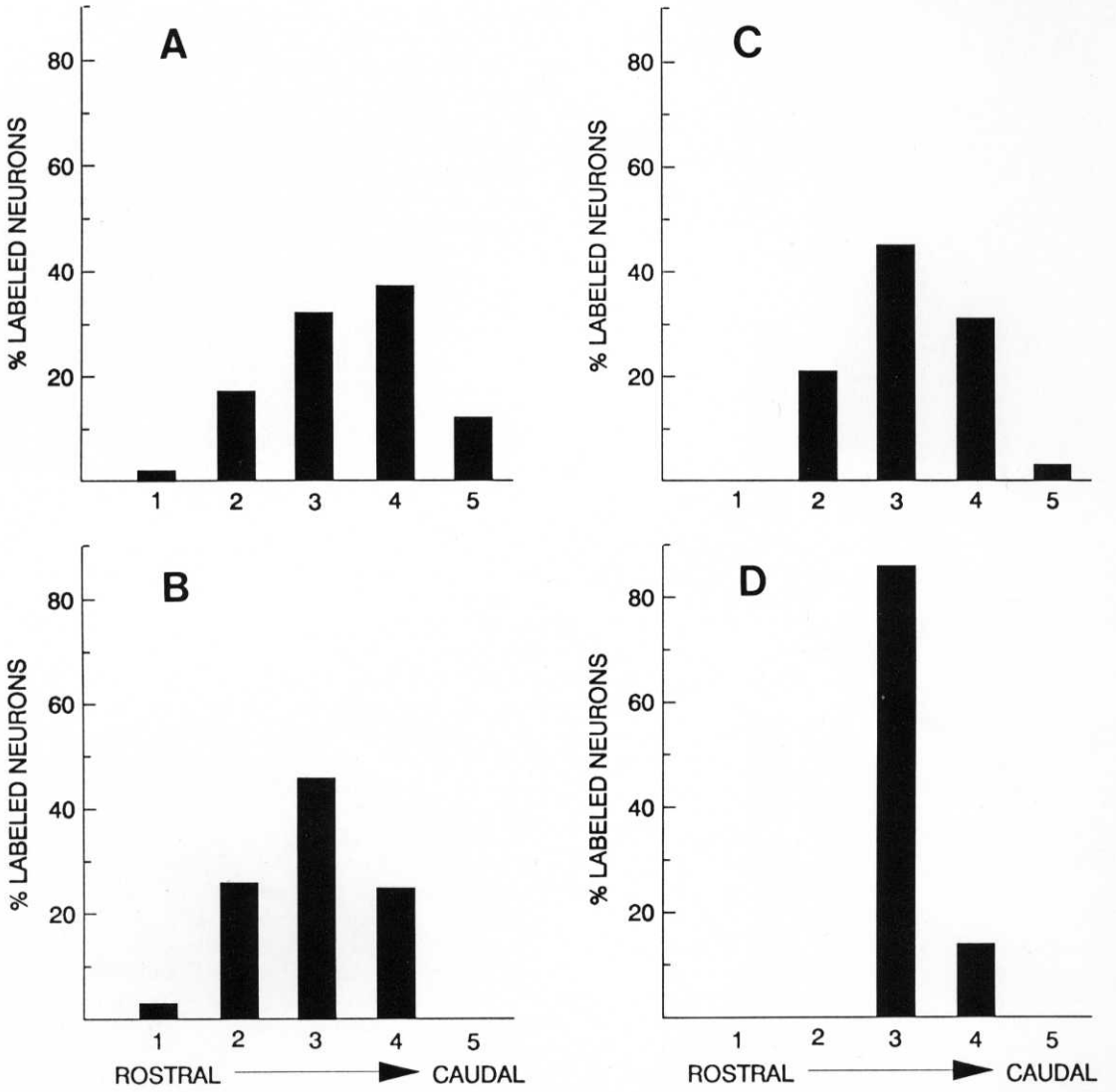

Fig. 15. The distribution of labeled neurons in the rostral (represented in category 1) and in progressively more caudal (5) sectors of the BL nucleus after injection of retrograde tracers in orbital (**A,** case 1, 2, 3b, 4, 3y, 5), ventrolateral (**B,** cases 6–8), medial (**C,** cases 9, 10, 3r, 11y, 11b), and dorsolateral (**D,** cases 12 and 13) prefrontal cortices.

cal) perirhinal cortex (Aggleton, '86; Saunders and Rosene, '88). The above evidence indicates that medially situated structures and at least portions of the lateral amygdaloid nucleus are connected preferentially with the least differentiated cortices, whereas the dorsal portion of the basolateral nucleus projects to somewhat more differentiated areas. These data suggest that the hypothesis that the amygdala evolved from a medial to lateral direction may be oversimplified. Further experiments are necessary to address this issue in the future.

Several investigators in the past have shown that destruction of the amygdala and the hippocampus results in severe impairments in memory in macaque monkeys (Mishkin, '78; Zola-Morgan et al., '82; Saunders et al., '84). Human studies indicate further that the medial parts of the amygdala along with the frontal and temporal lobes are the first to atrophy in some degenerative disorders such as senile dementia where memory processes are disrupted (Brockhaus, '40; Hooper and Vogel, '76; Herzog and Kemper, '80). If limbic structures have a central role in mnemonic processes, it is possible that those amygdaloid structures, which are connected with limbic cortices in the frontal and temporal cortices, may have a pivotal role in memory.

The present data showed some qualitative and topographic differences in the origin of projections to basoventral and mediodorsal prefrontal sites. In a previous study we showed that cortical projections to basoventral and to mediodorsal prefrontal cortices differ as well. The pattern of projections from visual, somatosensory, motor, and perhaps other cortical systems supports a discriminative role for basoventral prefrontal areas, whereas mediodorsal regions may be involved in spatial tasks and postural mechanisms (Barbas and Pandya, '87; Barbas, '88b); this

hypothesis is consistent with behavioral and physiologic data (Mishkin and Manning, '78; Voytko, '85; Bachevalier and Mishkin, '86; Vaadia et al., '86; Mishkin and Bachevalier, '86). By analogy, the amygdala, which has stronger connections with the basoventral prefrontal regions and receives robust projections from sensory cortices, may have a role in aspects of discriminative functions as well. In fact, behavioral experiments indicate that the amygdala has a role in cross-modal tasks, and in associating stimuli with reward (Spiegler and Mishkin, '81; Murray and Mishkin, '85; Gaffan and Harrison, '87). In contrast, mediodorsal prefrontal cortices, which are associated with spatial functions, have fewer links with the amygdala. It is thus reasonable to expect that overall the amygdala may have a comparatively smaller role in spatial tasks than in discriminative functions. Spatial functions may be supported largely by the hippocampal formation (Parkinson et al., '88; Gaffan and Harrison, '89), which is connected with the medial prefrontal cortices (Adey and Mayer, '52; Rosene and Van Hoesen, '77, '87 for review; personal observations).

The segregation of functions supported by the amygdala and the hippocampus seems, however, to be only partial. For example, behavioral data suggest that combined lesions of the amygdala and the hippocampus may be necessary to disrupt some mnemonic processes (Mishkin, '78; Zola-Morgan et al., '82; Saunders et al., '84; Zola-Morgan et al., '89). On the basis of anatomic data we suggest that subsectors of the amygdala may have a bias for different tasks. This hypothesis is supported by the preferential connections of medially situated amygdaloid structures with two systems implicated in spatial functions. One of these includes medial prefrontal cortices, as shown in this study. The other involves the hippocampus, which is also connected preferentially with amygdaloid nuclei located medially, such as the basomedial and the cortical (Van Hoesen, '81; Amaral, '85; Aggleton, '86; Saunders et al., '88). Taken together the above data suggest that if the amygdala participates in spatial functions it may do so preferentially via its medial sectors. Information on the origin and topography of amygdaloid projections directed to prefrontal cortices which have a bias for discriminative or spatial functions may allow the design of tasks to test specific aspects of mnemonic functions supported by the amygdala versus the hippocampus, on one hand, and by subsectors of the amygdala, on the other.

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