

# Differential Projections of the Infralimbic and Prelimbic Cortex in the Rat

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**KEY WORDS** agranular insular cortex; claustrum; nucleus accumbens; nucleus reuniens; prelimbic circuit; visceromotor activity; working memory

**ABSTRACT** The medial prefrontal cortex has been associated with diverse functions including attentional processes, visceromotor activity, decision-making, goal-directed behavior, and working memory. The present report compares and contrasts projections from the infralimbic (IL) and prelimbic (PL) cortices in the rat by using the anterograde anatomical tracer, *Phaseolus vulgaris*-leucoagglutinin. With the exception of common projections to parts of the orbitomedial prefrontal cortex, olfactory forebrain, and midline thalamus, PL and IL distribute very differently throughout the brain. Main projection sites of IL are: 1) the lateral septum, bed nucleus of stria terminalis, medial and lateral preoptic nuclei, substantia innominata, and endopiriform nuclei of the basal forebrain; 2) the medial, basomedial, central, and cortical nuclei of amygdala; 3) the dorsomedial, lateral, perifornical, posterior, and supramammillary nuclei of hypothalamus; and 4) the parabrachial and solitary nuclei of the brainstem. By contrast, PL projects at best sparingly to each of these structures. Main projection sites of PL are: the agranular insular cortex, claustrum, nucleus accumbens, olfactory tubercle, the paraventricular, mediodorsal, and reuniens nuclei of thalamus, the capsular part of the central nucleus and the basolateral nucleus of amygdala, and the dorsal and median raphe nuclei of the brainstem. As discussed herein, the pattern of IL projections is consistent with a role for IL in the control of visceral/autonomic activity homologous to the orbitomedial prefrontal cortex of primates, whereas those of PL are consistent with a role for PL in limbic-cognitive functions homologous to the dorsolateral prefrontal cortex of primates. **Synapse 51:32–58, 2004.** © 2003 Wiley-Liss, Inc.

## INTRODUCTION

The medial prefrontal cortex (mPFC) in the rat consists of four main subdivisions which, from dorsal to ventral, are the medial agranular (AGm) (or medial precentral), the anterior cingulate (AC) (dorsal and ventral divisions), the prelimbic (PL), and the infralimbic (IL) cortices (Berendse and Groenewegen, 1991; Ray and Price, 1992; Price, 1995; Swanson, 1998; Ongur and Price, 2000).

The mPFC has been associated with diverse functions including oculomotor control (frontal eye fields), attentional processes, visceromotor activity, decision-making, goal-directed behavior, and working memory (Goldman-Rakic, 1987, 1994; Fuster, 1989; Neafsey et al., 1986a; Kolb, 1990; Neafsey, 1990; Petrides, 1995, 1998). The various subdivisions of mPFC appear to serve separate and distinct functions. For instance, dorsal regions of mPFC (AGm and AC) have been implicated in various motor behaviors, while ventral regions of mPFC (PL and IL) have been associated with diverse emotional, cognitive, and mnemonic processes.

Early reports in rats showed that stimulation of AGm/AC generated eye movements (Hall and Lindholm, 1974; Donoghue and Wise, 1982), which together with the demonstration that AGm/AC projects to oculomotor sites (Beckstead, 1979; Hardy and Leichnetz, 1981; Neafsey et al., 1986a; Leichnetz and Gonzalo-Ruiz, 1987; Leichnetz et al., 1987; Reep et al., 1987; Stuesse and Newman, 1990), led to the proposal that AGm/AC of rats was equivalent to the frontal eye fields (FEF) of primates (Leonard, 1969; Leichnetz and Gonzalo-Ruiz, 1987; Reep et al., 1984, 1987; Guandalini, 1998). Subsequent reports confirmed AGm involvement in eye movement control, and further

Contract grant sponsor: NIMH; Contract grant numbers: MH63519, MH01476.

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Received 8 May 2003; Accepted 31 July 2003

DOI 10.1002/syn.10279

showed that AGm stimulation produced other types of movements including those of the vibrissa, head, and hindlimbs (Neafsey and Sievert, 1982; Sanderson et al., 1984; Sinnamon and Galer, 1984; Gioanni and Lamarche, 1985; Neafsey et al., 1986a). Accordingly, it has been variously proposed that the AGm/AC of rats is homologous to the FEF, supplementary motor, and premotor cortices of primates (Neafsey et al., 1986a; Passingham et al., 1988; Reep et al., 1987, 1990).

In contrast to motor-associated properties of the dorsal mPFC, the ventral mPFC (IL and PL) has been anatomically and functionally linked with the limbic system. For

instance, the ventral mPFC (or IL) has been shown to profoundly influence visceral/autonomic activity. IL stimulation produces changes in respiration, gastrointestinal motility, heart rate, and blood pressure (Terreberry and Neafsey, 1983; Burns and Wyss, 1985; Hurley-Gius and Neafsey, 1986; Verberne et al., 1987; Hardy and Holmes, 1988). IL has been viewed as a visceromotor center (Hurley-Gius and Neafsey, 1986; Neafsey, 1990), homologous to the orbitomedial prefrontal cortex of primates (Barbas, 1995, 2000; Groenewegen and Uylings, 2000).

The ventral mPFC (primarily PL) has also been implicated in cognitive processes. Ventral mPFC lesions

#### Abbreviations

AA	anterior area of amygdala	MO	medial orbital cortex
AC	anterior cingulate cortex, dorsal division	MPN	medial preoptic nucleus
ACC	nucleus accumbens	MPO	medial preoptic area
AGm	medial agranular (prefrontal) cortex	MR	median raphe nucleus
AGl	lateral agranular (prefrontal) cortex	MRF	mesencephalic reticular formation
AHN	anterior hypothalamic nucleus	MS	medial septum
AI,d,p,v	agranular insular cortex, dorsal, posterior, ventral divisions	MT	mammillothalamic tract
AM	anteromedial nucleus of thalamus	NLL	nucleus of lateral lemniscus
AON,m,v	anterior olfactory nucleus, medial, ventral parts	NPC	nucleus of posterior commissure
AV	anteroventral nucleus of thalamus	NTS	nucleus of solitary tract
APN	anterior pretectal nucleus	N7	facial nucleus
BLA	basolateral nucleus of amygdala	OC	occipital cortex
BMA	basomedial nucleus of amygdala	OT	olfactory tubercle
BST	bed nucleus of stria terminalis	PAG,v	periaqueductal gray, ventral division
C	cerebellum	PAR	parasubiculum
CA1	field CA1, Ammon's horn	PAR	parabrachial nucleus, medial, lateral parts
CA3	field CA3, Ammon's horn	PCO	precommissural nucleus
CEA,c	central nucleus of amygdala, capsular part	PFx	perifornical region of hypothalamus
CEM	central medial nucleus of thalamus	PH	posterior nucleus of hypothalamus
CLA	claustrum	PIR	piriform cortex
COA	cortical nucleus of amygdala	PL	prelimbic cortex
C-P	caudate-putamen, striatum	Pmd	dorsal premammillary nucleus
CU	nucleus cuneiformis	PMv	ventral premammillary nucleus
DB,h,v	nucleus of the diagonal band, horizontal, vertical limbs	PN	nucleus of pons
DG	dentate gyrus	PO	posterior nucleus of thalamus
DMH	dorsomedial nucleus of hypothalamus	POA	posterior nucleus of amygdala
DR	dorsal raphe nucleus	PRC	perirhinal cortex
EC	entorhinal cortex	PRE	presubiculum
ECT	ectorhinal cortex	PT	paratenial nucleus of thalamus
EN	endopiriform nucleus	PV,p	paraventricular nucleus of thalamus, posterior part
FI	fimbria of hippocampus	RE	nucleus reuniens of thalamus
FP,m,l	frontal polar cortex, medial, lateral divisions	RH	rhomboid nucleus of thalamus
FR	fasciculus retroflexus	RN	red nucleus
GI	granular insular cortex	RPO	nucleus reticularis pontis oralis
GP	globus pallidus	RR	retrobulbar area
HF	hippocampal formation	RSC	retrosplenial cortex
IAM	interanteromedial nucleus of thalamus	RT	reticular nucleus of thalamus
IC	inferior colliculus	RTG	reticular tegmental nucleus
IL	infralimbic cortex	SC	superior colliculus
INC	insular cortex	SF	septofimbrial nucleus
IP	interpeduncular nucleus	SI	substantia innominata
IMD	intermediodorsal nucleus of thalamus	SLN	supralemniscal nucleus (B9)
LA	lateral nucleus of amygdala	SME	submedial nucleus of thalamus
LD	lateral dorsal nucleus of thalamus	SN,c,r	substantia nigra, pars compacta, pars reticulata
LGd	lateral geniculate nucleus, dorsal division	SSI	primary somatosensory cortex
LH	lateral habenula	SSII	secondary somatosensory cortex
LHy	lateral hypothalamic area	SUB,d	subiculum, dorsal part
LOT	lateral olfactory tract	SUM	supramammillary nucleus
LP	lateral posterior nucleus of thalamus	TE	temporal cortex
LPO	lateral preoptic area	TT,d,v	taenia tecta, dorsal, ventral parts
LS	lateral septal nucleus	VAL	ventral anterior-lateral complex of thalamus
LV	lateral ventricle	VB	ventrobasal complex of thalamus
MA	magnocellular preoptic nucleus	VMH	ventromedial nucleus of hypothalamus
MB	mammillary bodies	VLO	ventral lateral orbital cortex
MD	mediodorsal nucleus of thalamus	VO	ventral orbital cortex
MEA	medial nucleus of amygdala	VT	ventral tegmental nucleus (Gudden)
MGv	medial geniculate nucleus, ventral division	VTA	ventral tegmental area
		ZI	zona incerta

(or PL lesions) have been shown to produce pronounced deficits in delayed response tasks (Brito and Brito, 1990; Seamans et al., 1995; Delatour and Gisquet-Verrier, 1996, 1999, 2000; Floresco et al., 1997; Ragozzino et al., 1998), similar to those seen with lesions of the dorsolateral PFC of primates (Kolb, 1984; Goldman-Rakic, 1987, 1994; Groenewegen and Uylings, 2000).

A view appears to be emerging that IL primarily serves a role in visceromotor functions and PL in cognitive processes. Despite apparent functional differences, IL and PL are often (or generally) treated as a single region (i.e., the ventral mPFC), with reportedly minor differences in their efferent projections. For instance, following an analysis of IL, PL, and anterior cingulate projections in rabbits, Buchanan et al. (1994) concluded that: "there were many similarities between the projections from the three cytoarchitectonic areas." In like manner, Takagishi and Chiba (1991) examined IL projections in the rat, compared their findings to an earlier description of PL projections in rats (Sesack et al., 1989), and reported that 26 of 27 sites receive common projections from IL and PL (see their fig. 10, p. 35). Finally, Price and co-workers (Floyd et al., 2000, 2001) recently demonstrated significantly overlapping IL and PL projections to the periaqueductal gray (PAG) and hypothalamus in rats, stating, for instance (Floyd et al., 2001) that: "Projections from rostral PL/IL targeted the rostrocaudal extent of the lateral hypothalamus"; and "Projections arising from the caudal PL/IL terminated within the dorsal hypothalamus."

In the present report, we examine, compare, and contrast projections from the IL and PL cortices in the rat and show, with few exceptions, that IL and PL distribute very differently throughout the brain. These differential projections undoubtedly reflect distinct functions for IL and PL.

## MATERIALS AND METHODS

Single injections of PHA-L were made into the IL or PL of 26 male Sprague-Dawley (Charles River, Wilmington, MA) rats weighing 275–325 g. These experiments were approved by the Florida Atlantic University Institutional Animal Care and Use Committee and conform to all federal regulations and the National Institutes of Health *Guidelines for the Care and Use of Laboratory Animals*.

Powdered lectin from *Phaseolus vulgaris*-leucoagglutinin was reconstituted to 2.5% in 0.05 M sodium phosphate buffer, pH 7.4. The PHA-L solution was iontophoretically deposited in the brains of anesthetized rats by means of a glass micropipette with an outside tip diameter of 40–60  $\mu\text{m}$ . Positive direct current (5–10  $\mu\text{A}$ ) was applied through a Grass stimulator (Model 88) coupled with a high-voltage stimulator (FHC, Bowdoinham, ME) at 2 sec "on" / 2 sec "off" intervals for 30–40 min. After a survival time of 7–10 days, animals were deeply anesthetized with sodium pentobarbital and perfused transcardially with a buffered saline wash (pH 7.4, 300

ml/animal) followed by fixative (2.5% paraformaldehyde, 0.05–0.1% glutaraldehyde in 0.05 M phosphate buffer, pH 7.4) (300–500 ml/animal), and then by 10% sucrose in the same phosphate buffer (150 ml/animal). The brains were removed and stored overnight at 4°C in 20% sucrose in the same phosphate buffer. On the following day, 40 or 50  $\mu\text{m}$  frozen sections were collected in phosphate-buffered saline (PBS, 0.9% sodium chloride in 0.01 M sodium phosphate buffer, pH 7.4) and incubated for 1 h in diluent (10% normal rabbit serum (Colorado Serum, Denver, CO) and 1% Triton X-100 (Sigma Chemicals, St. Louis, MO), in PBS). Sections were then incubated overnight (14–17 h) at 4°C in primary antiserum directed against PHA-L (biotinylated goat anti-PHA-L, Vector Laboratories, Burlingame, CA) at a dilution of 1:500 in diluent. The next day, sections were washed 5 times for 5 min each ( $5 \times 5$  min) in PBS, and then incubated in the second antiserum (rabbit anti-sheep IgG, Vector Labs) at a dilution of 1:500 in diluent for 2 h. Sections were rinsed again ( $5 \times 5$  min) and incubated with peroxidase-antiperoxidase (goat origin, Sternberger Monoclonals, Baltimore, MD) at a dilution of 1:250 for 2 h. The last two incubations were repeated (double-bridge procedure) with  $5 \times 5$  min rinses following each incubation for 1 h each. After  $5 \times 5$  min rinses the sections were incubated in 0.05% 3,3'-diaminobenzidine (DAB) in PBS for 10 min, followed by a second, 5-min DAB (same concentration) incubation to which 0.018%  $\text{H}_2\text{O}_2$  had been added. Sections were then rinsed again in PBS ( $3 \times 1$  min) and mounted onto chrome-alum gelatin-coated slides. An adjacent series of sections was stained with cresyl violet for anatomical reference.

Sections were examined using light and darkfield optics. PHA-L-labeled cells (at injection sites) and fibers were plotted onto maps constructed from adjacent Nissl-stained sections. The main criteria used to distinguish labeled terminals from fibers of passage were: 1) the presence or essential absence of axon/terminal specializations; and 2) the degree of axonal branching. Terminal sites were typically characterized by a dense array of highly branched axons containing numerous specializations (varicosities, terminal boutons), whereas passing fibers exhibited minimal branching and contained few specializations. The lightfield photomicrographs of the injection sites were taken with a Nikon DXM1200 camera mounted on a Nikon Eclipse E600 microscope and enhanced (contrast and brightness) using Adobe PhotoShop 7.0 (Mountain View, CA), while the darkfield photomicrographs of labeled fibers were taken with a Nikon FX-35A 35 mm camera.

## RESULTS

The patterns of distribution of labeled fibers throughout the brain with injections in the infralimbic (IL) and prelimbic (PL) cortices are described. Two cases are depicted and described in detail: one with an

injection in IL (case 701) (Fig. 1A) and the other with an injection in PL (case 668) (Fig. 1B,C). The patterns of labeling obtained with the schematically illustrated cases (see below) are representative of patterns found with nonillustrated cases.

### Infralimbic cortex: case 701

Figure 2 schematically depicts patterns of labeling throughout the brain following a PHA-L injection in the infralimbic cortex (Fig. 2C). PHA-L-filled cells were primarily localized to layer 6 of IL, with some extension to layer 5, mainly ventrally in layer 5 (Fig. 1A).

Labeled fibers coursed forward from the site of injection to distribute to frontal polar regions of cortex and olfactory structures (Fig. 2A). Labeled fibers spread dorsoventrally throughout the medial wall of mPFC terminating in the medial frontal polar cortex (FPm), the rostral prelimbic cortex, and the medial orbital cortex (MO). Significant numbers also extended laterally from MO to distribute to the ventrolateral (VLO) and lateral (LO) orbital cortices. Labeling was heaviest in ventral FPm and PL and largely restricted to layers 1 and 5/6 of these regions. The primary olfactory targets were the anterior olfactory nucleus (AONm) and the dorsally adjacent dorsal tania tecta (TTd) (layers 2–4), with some extension to the ventral tania tecta (TTv) (Fig. 2A). Labeling was considerably stronger ipsilaterally (left side) than contralaterally.

Further caudally (Fig. 2B), labeled fibers continued to occupy most of the medial wall of mPFC, mainly confined to the anterior cingulate (AC), PL, and medial orbital cortices. Although labeling spread to all layers of cortex, it was most densely concentrated in layers 1 and 5/6 of mPFC. A few labeled fibers were observed laterally in VLO. The AONm and TTv were moderately labeled.

Like rostrally (Fig. 2A,B), the principal destination of labeled fibers at the site of injection (Fig. 2C) was regions of the cortex and olfactory structures. The AC, PL, and IL were heavily labeled; the dorsal agranular insular cortex (AId), rostral endopiriform nucleus (EN), and anterior ventral olfactory nucleus (AONv) were moderately labeled. As depicted (Fig. 2C), there was a notable absence of labeling in nucleus accumbens (ACC).

Labeled fibers descended from the site of injection primarily through dorsomedial aspects of cortex and through the medial one-third of the striatum (C-P) to distribute strongly to AC, IL, TTd, and anterolateral regions of the septum, and less heavily to the olfactory tubercle (OT), ventral agranular insular cortex (AIV), and EN (bilaterally) (Fig. 2D,E). The ACC was lightly labeled ipsilaterally. Further caudally, labeled fibers, grouped in small bundles, descended through the medial striatum (Fig. 2E,F), distributing en route to dorsal and ventral parts of medial C-P, and beyond the striatum to the lateral septum (LS),

OT, EN, the posterior agranular insular cortex (AIP), and the horizontal limb of diagonal band nucleus (DBh). Labeled axons appeared to mainly traverse the medial ACC bound for caudal regions of the basal forebrain (Fig. 2E,F).

At the mid-septum (Fig. 2G), labeled fibers spread widely over the basal forebrain, strongly targeting anterior regions of the bed nucleus of stria terminalis (BST), the substantia innominata (SI), DBh, and EN, and, moderately, the medial C-P, AC, and LS. At the caudal septum (Fig. 2H,I), labeling was mainly confined to structures of the medial basal forebrain and anterior hypothalamus. Major sites of termination were BST (all divisions), EN, lateral aspects of the medial preoptic area (MPO), and the lateral preoptic area (LPO), with extensions caudally to the lateral hypothalamus (LHy) (Fig. 2I). This pattern of labeling is depicted in the photomontage of Figure 3. Labeled fibers surrounded but did not appear to terminate in the magnocellular preoptic nucleus (MA), while some distributed to the medial preoptic nucleus (MPN) (Fig. 2H). Only scattered labeling was observed in the cortex, essentially restricted to AC.

The main route of descent of labeled fibers through the diencephalon was the medial forebrain bundle (MFB). A major contingent of labeled axons coursed dorsomedially from the MFB into the thalamus to terminate massively in the paratenial nucleus (PT), medial and central divisions of the mediodorsal nucleus (MDm and MDc) and nucleus reuniens (RE) (Fig. 2J,K). Others continuing to descend with the MFB distributed terminally in transit to lateral (LHy) and perifornical (PFx) regions of the hypothalamus. The anterior amygdala was fairly uniformly labeled (Fig. 2J-L); labeling was densest in the medial, cortical (anterior and posterolateral parts), and central (medial and capsular regions) nuclei (Fig. 4). The caudal pole of BST, zona incerta (ZI), EN, and the rhomboid (RH) and central medial (CEM) nuclei of thalamus were moderately labeled (Fig. 2J,K).

Further caudally in the diencephalon (Fig. 2L,M), labeling was largely confined to the midline thalamus, hypothalamus, and amygdala; that is, 1) to the MD complex, dorsally, and RE, ventrally, of the thalamus; 2) to the perifornical region, LHy, and dorsomedial nuclei of the hypothalamus; and 3) to the medial, basomedial, and central (medial and capsular divisions) nuclei of the amygdala.

Labeling thinned considerably at caudal levels of the diencephalon (Fig. 2N,O). Moderately dense numbers of labeled fibers, however, were present in the posterior paraventricular (PVp), intermediodorsal (IMD), and medial aspects of the parafascicular (PF) nuclei of thalamus, as well as in the lateral, posterior, and supramammillary (SUM) nuclei of the hypothalamus. Caudal regions of the amygdala were sparsely labeled. Figure 5 shows significant labeling

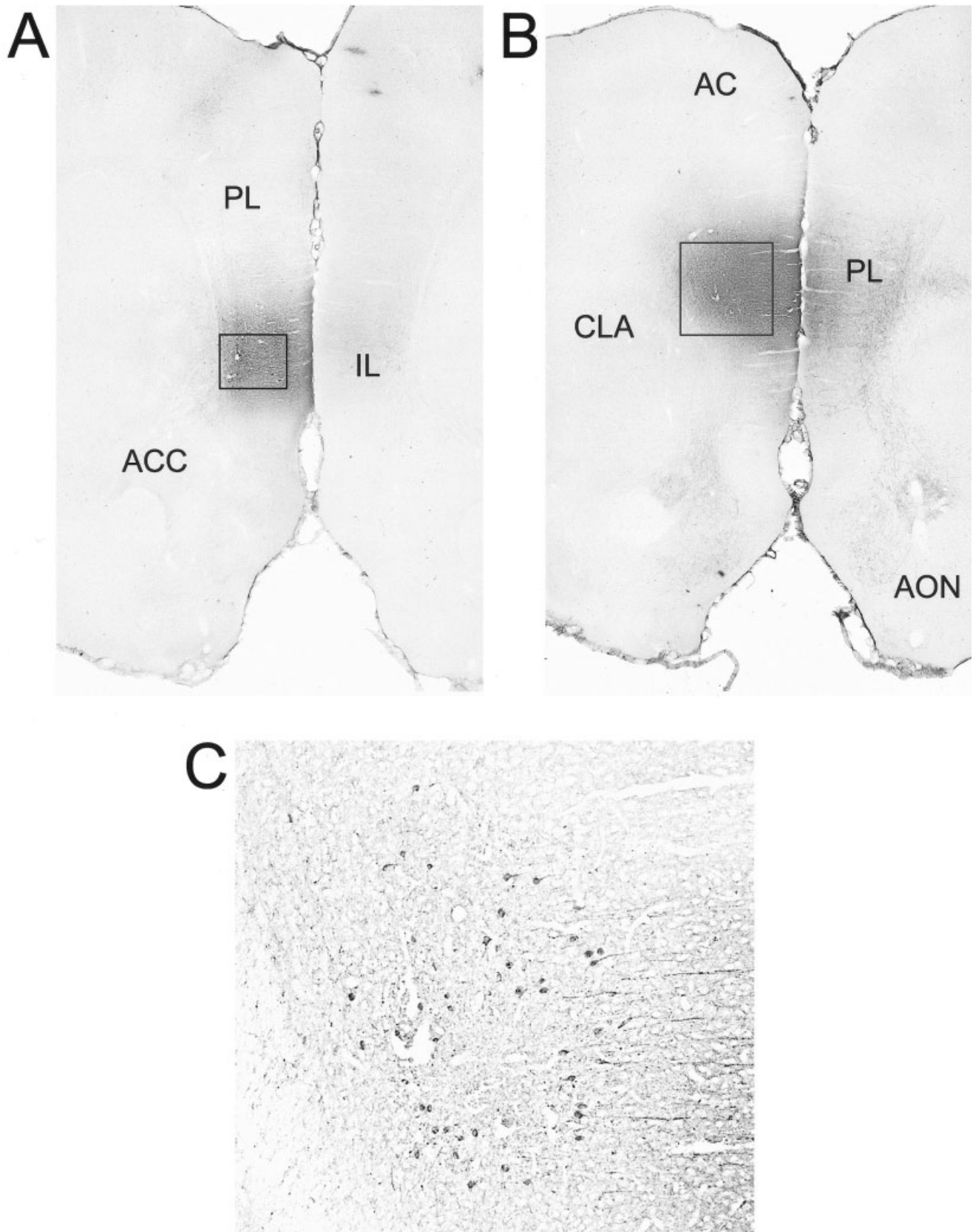


Fig. 1. **A,B:** Low-magnification lightfield photomicrographs showing the locations of *Phaseolus vulgaris*-leucoagglutinin (PHA-L) injections in the infralimbic (**A**) and prelimbic (**B**) cortices in the rat. Rectangles indicate the areas of PHA-L-filled cells in the respective injections. **C:** High-magnification lightfield photomicrograph showing

PHA-L filled cells in the prelimbic cortex (corresponds to rectangle in **B**). Note PHA-L labeled fibers coursing from the sites of injection to respective contralateral fields (**A,B**) and particularly prominent fibers from the prelimbic cortex (**B**) to the anterior olfactory nucleus, ipsilaterally and contralaterally. For abbreviations, see list.

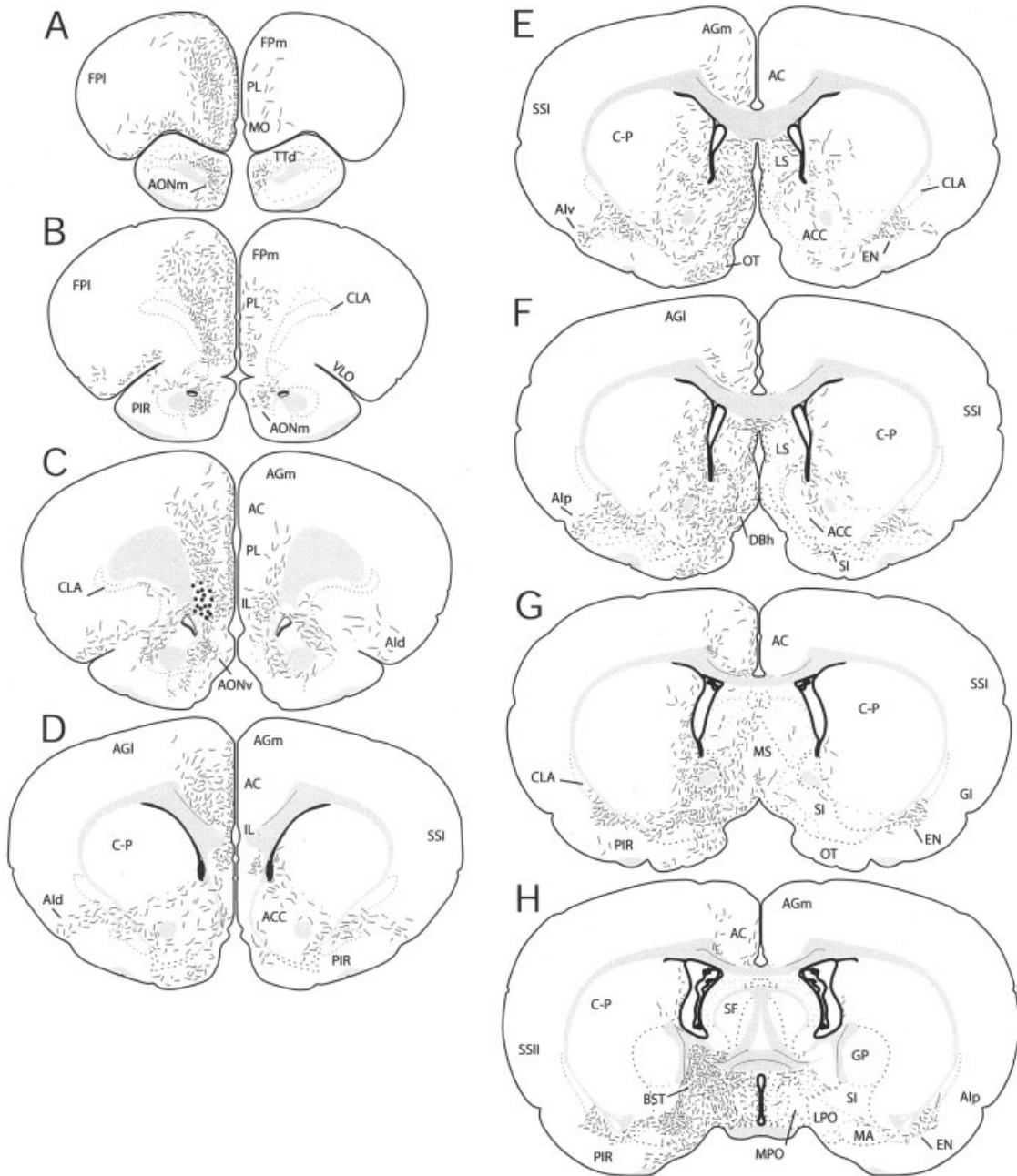


Fig. 2. Schematic representation of labeling present in selected sections through the forebrain and rostral brainstem (A-R) produced by a PHA-L injection (dots in C) in the infralimbic cortex (case 701). Sections modified from the rat atlas of Swanson (1998). For abbreviations, see list. (Figure 2 continued p. 38-39).

along the midline within PVp, IMD, and PH (Fig. 5A) as well as caudally in SUM (Fig. 5B,C).

Labeling continued to decline at the level of the brainstem (Fig. 2P-R). Main brainstem targets were medial/ventromedial regions of the periaqueductal gray (PAG), the substantia nigra-pars compacta (SNc), the interpeduncular nucleus, and the medial and lateral parabrachial nuclei (Fig. 2P,Q). The ventral tegmental area (VTA), dorsal raphe nucleus, Barrington's nucleus, the nucleus ambiguus (not

shown), and nucleus of the solitary tract (not shown) were lightly to moderately labeled. Finally, at caudal levels of the cortex labeling was essentially confined to the lateral entorhinal cortex (bilaterally) (Fig. 2P-R).

**Differences in rostral and caudal IL projections**

Although patterns of projections from the rostral and caudal IL were largely similar, there were some notable differences. Rostral regions of IL distribute

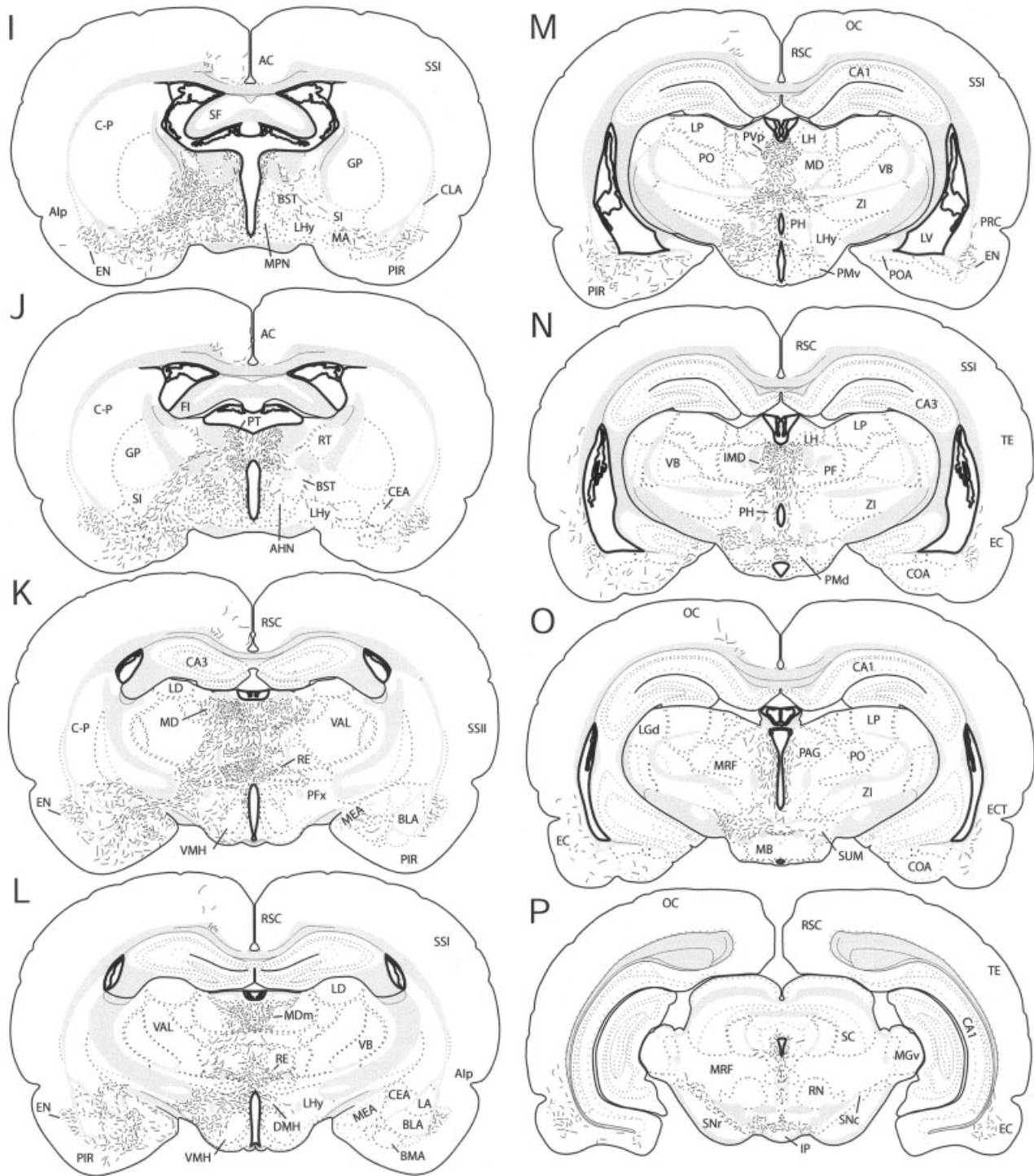


Figure 2 (Continued).

more heavily than caudal regions to the posterior insular cortex, the shell of ACC, BST, the central and basomedial nuclei of the amygdala, MDm, and EC. On the other hand, the caudal IL projects more heavily than the rostral IL to the lateral septum and DBh, the anterior hypothalamus, the supramammil-

lary nucleus, and the diencephalic and mesencephalic periventricular gray.

**Prelimbic cortex: case 668**

Figure 6 schematically depicts the distribution of labeled fibers throughout the brain following a

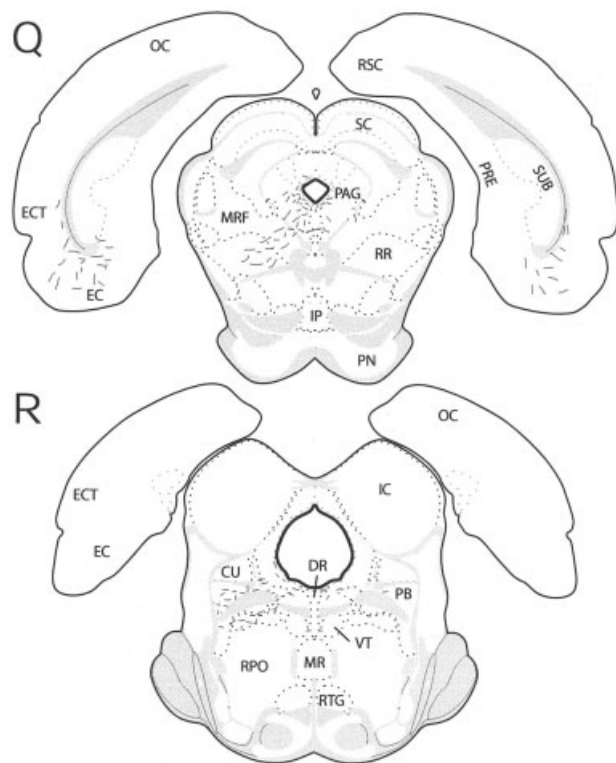


Figure 2 (Continued).

PHA-L injection in the prelimbic cortex. As shown (Fig. 1B,C), PHA-L-filled cells were restricted to layers 5 and 6 of PL.

Labeled fibers coursed forward from the site of injection (Fig. 6B,C) to distribute to the medial orbitofrontal cortex and olfactory structures of the anterior forebrain (Fig. 6A). Main terminal sites were FPM, anterior PL and MO of the medial prefrontal cortex, and the dorsal and ventral tania tecta, anterior piriform cortex, and anterior olfactory nucleus of the olfactory forebrain (Fig. 7A,B). Layer 1 of VO and VLO was lightly to moderately labeled.

Labeled fibers spread in several directions from the site of injection (Fig. 6B); that is, locally to PL, AC, and IL, ventrally to the anterior olfactory nucleus, TTd, TTv, and VO, and laterally to AId. Labeling was fairly uniform throughout all layers of AC, PL, and IL, but restricted to layers 5/6 of VO. Figure 8 depicts labeling in the contralateral mPFC, mainly localized to PL, at two levels of the anterior forebrain.

Further caudally (Fig. 6C), labeling remained pronounced in PL and IL, mainly concentrated in layers 1–3 and 6, bilaterally. A prominent bundle of labeled axons coursed laterally from PL to densely innervate the dorsal and ventral agranular insular cortices, stronger contralaterally (right side) than ipsilaterally. In addition, a dense array of labeled fibers capped the anterior commissure, localized to AONv and to the anterior part of nucleus accumbens. The OT was mod-

erately labeled. This pattern of labeling is depicted in the photomontage of Figure 9.

Labeled fibers descended from the site of injection mainly through dorsomedial aspects of the cortex and through the medial striatum, distributing en route to AC and to dorsomedial parts of C-P, respectively, and beyond the striatum to ACC, OT, the claustrum (CLA) and AId (Fig. 6D,E). Both the shell and core of ACC were densely labeled. Figure 10 depicts pronounced labeling contralaterally in ACC, CLA and deep layers (5 and 6) of AId.

The primary targets of labeled fibers at the level of the septum (Fig. 6F,G) were AC, medial C-P, substantia innominata, CLA, OT, and DBh. C-P and CLA were heavily labeled; the other sites were lightly to moderately labeled. Unlike pronounced labeling rostrally in ACC, there was a virtual absence of labeled fibers in the caudal pole (medial shell) of ACC.

At the rostral diencephalon (Fig. 6H,I), a large contingent of labeled axons swept dorsomedially from the internal capsule into the thalamus to distribute heavily to the anterior PT, RE, and the medial division of MD, and lightly to the paraventricular nucleus of thalamus; a second group took a more ventral course terminating lightly to moderately in LHy, CLA, and the basolateral nucleus of the amygdala. SI and ZI were sparsely labeled.

At mid-levels of the diencephalon (Fig. 6J,K), labeling was mainly restricted to MD and RE of thalamus and parts of the amygdala. Medial and lateral divisions of MD were heavily labeled; MDc was essentially devoid of labeled fibers. Within the amygdala, labeling was virtually confined to the central nucleus (dorsal capsular and lateral parts) and the basolateral nucleus—stronger contralaterally (right side) than ipsilaterally. Figure 11 depicts labeling contralaterally in CE and BLA at three levels of the amygdala. At these same levels, ZI, LHy, and CLA, were lightly to moderately labeled.

The virtually exclusive targets of labeled fibers at the caudal diencephalon (Fig. 6L,M) were the midline thalamus and the hypothalamus; that is, the lateral habenula, posterior PV (PVp), IMD, medial PF, and the central medial nucleus (CEM) of the thalamus, and LHy, the posterior nucleus (PH), the dorsal premammillary nucleus and SUM of the hypothalamus. The most heavily labeled sites were PVp, IMD, CEM, and PH.

Labeled fibers primarily reached the brainstem via the mammillary peduncle (MP) (Fig. 6M–P). Significant numbers exited laterally from MP to moderately innervate SNc, while others continued caudally with MP to distribute to VTA, IP, the supramammillary nucleus (B9), and the median raphe nucleus. A branch of this latter bundle arched dorsolaterally through the pontine tegmentum to fairly densely innervate ventromedial and lateral regions of PAG (including the pre-



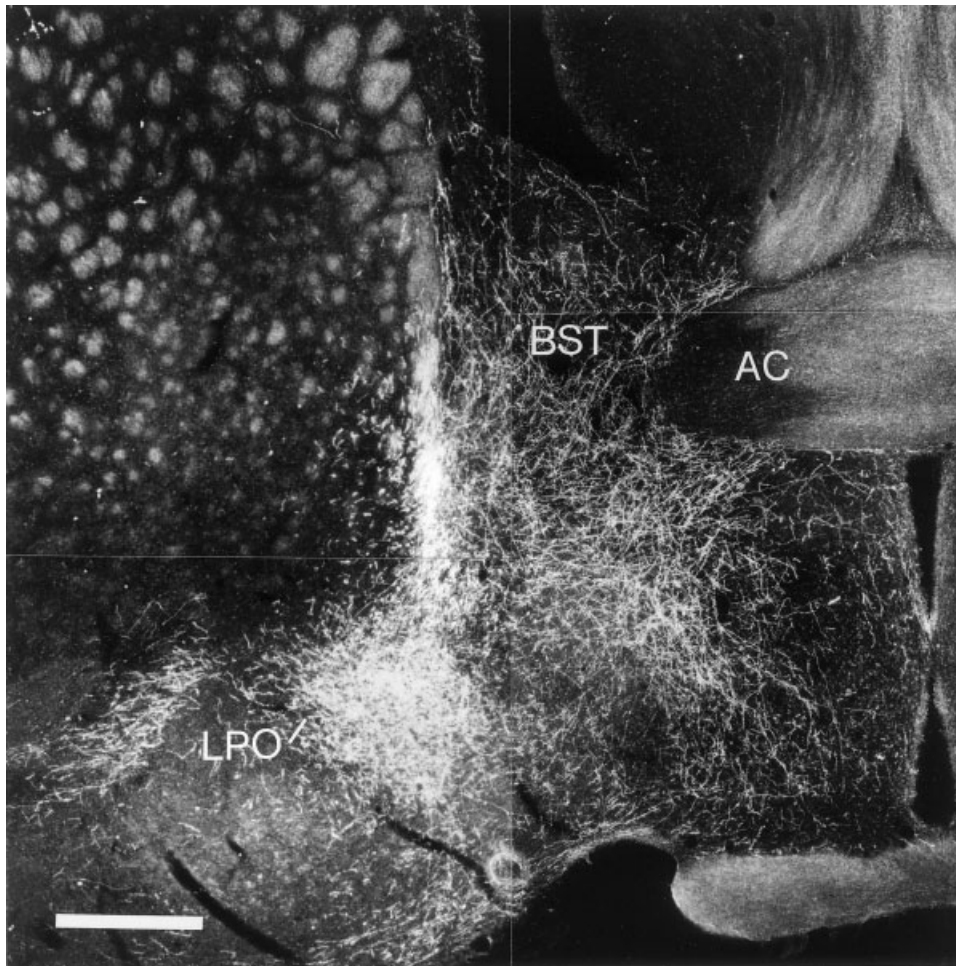


Fig. 3. Darkfield photomicrograph of a transverse section through the forebrain showing patterns of labeling in the basal forebrain produced by an injection in the infralimbic cortex (case 701). Note dense terminal labeling in the bed nucleus of the stria terminalis (BST), the ventral part of the lateral preoptic area (LPO), and the medially adjacent medial preoptic area. Scale bar = 600  $\mu$ m.

commissural nucleus) and the dorsal raphe nucleus. Finally, moderate labeling was observed in the piriform, perirhinal, and entorhinal cortices at caudal levels of the cortex.

#### Differences in rostral/caudal and dorsal/ventral PL projections

There were distinct differences in projections from the rostral and caudal PL. The rostral PL distributes more heavily than the caudal PL to the agranular insular cortex (deep and superficial layers), the entorhinal cortex, the core of ACC, the basolateral and central nuclei of the amygdala, MDm, SUM, PVp, and the dorsal raphe nucleus. On the other hand, the caudal PL projects more heavily than the rostral PL to the anterior cingulate cortex (supracollasal part), lateral septum, the anterior nucleus of the hypothalamus, the anteromedial and interanteromedial nuclei of the thalamus, MDl, RE, and the supralemniscal nucleus (B9). In addition, the rostral PL distributes fairly selectively to ventrolateral regions of the PAG and the caudal PL to the dorsolateral PAG.

Differences in dorsal and ventral PL projections largely depended on the proximity of injections to

adjacent regions of the mPFC (AC for the dorsal PL; IL for the ventral PL); that is, the closer injections were to neighboring regions the stronger were common projections with respective regions. For instance, dorsal PL fibers distributed heavily to the posterior cingulate/retrosplenial cortex and the lateral MD (mirroring AC), while the ventral PL projected heavily to the DBh, MPO, and medial MD (mirroring IL). Based on previous reports of differential dorsal and ventral PL projections to the ventral striatum (nucleus accumbens) (Berendse et al., 1992; Groenewegen et al., 1999), we carefully examined PL projections to ACC and found only a slight tendency of dorsal PL fibers to distribute more heavily to the core than shell of ACC and ventral PL fibers to distribute more densely to the shell than core of ACC, rather than a clear separation of dorsal and ventral PL projections to parts of ACC as previously described (Berendse et al., 1992).

#### DISCUSSION

We compared and contrasted projections from the infralimbic and prelimbic cortices in the rat. With the exception of projections to the thalamus and

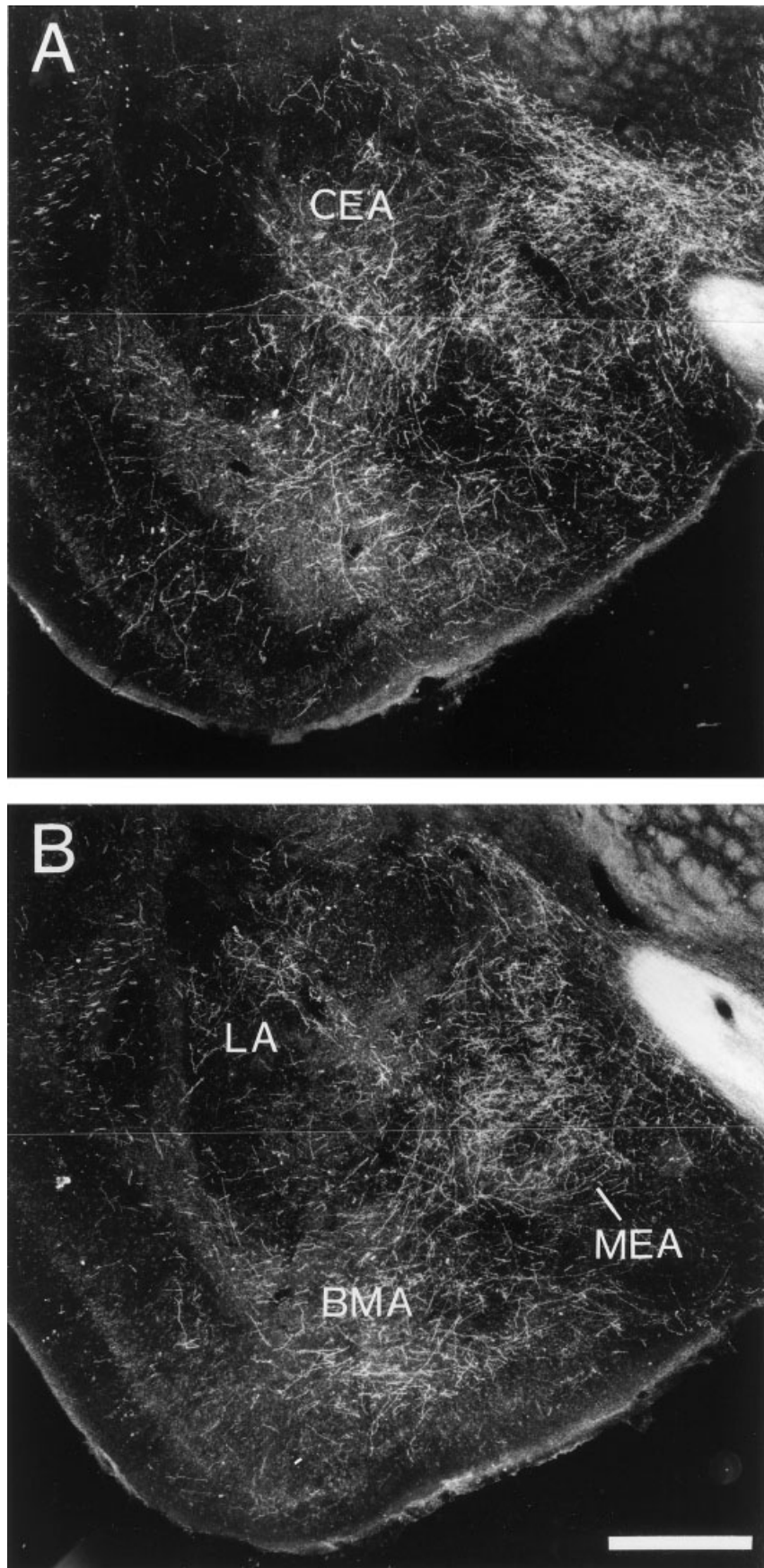


Fig. 4. Darkfield photomicrograph of a transverse section through the forebrain showing patterns of labeling in the amygdala produced by an injection in the infralimbic cortex (case 701). Note pronounced labeling in the central (A), medial (A,B), and basomedial (A,B) nuclei, and an essential absence of labeling in the lateral and basolateral nuclei, lateral to the central nucleus. Scale bar = 600  $\mu$ m.

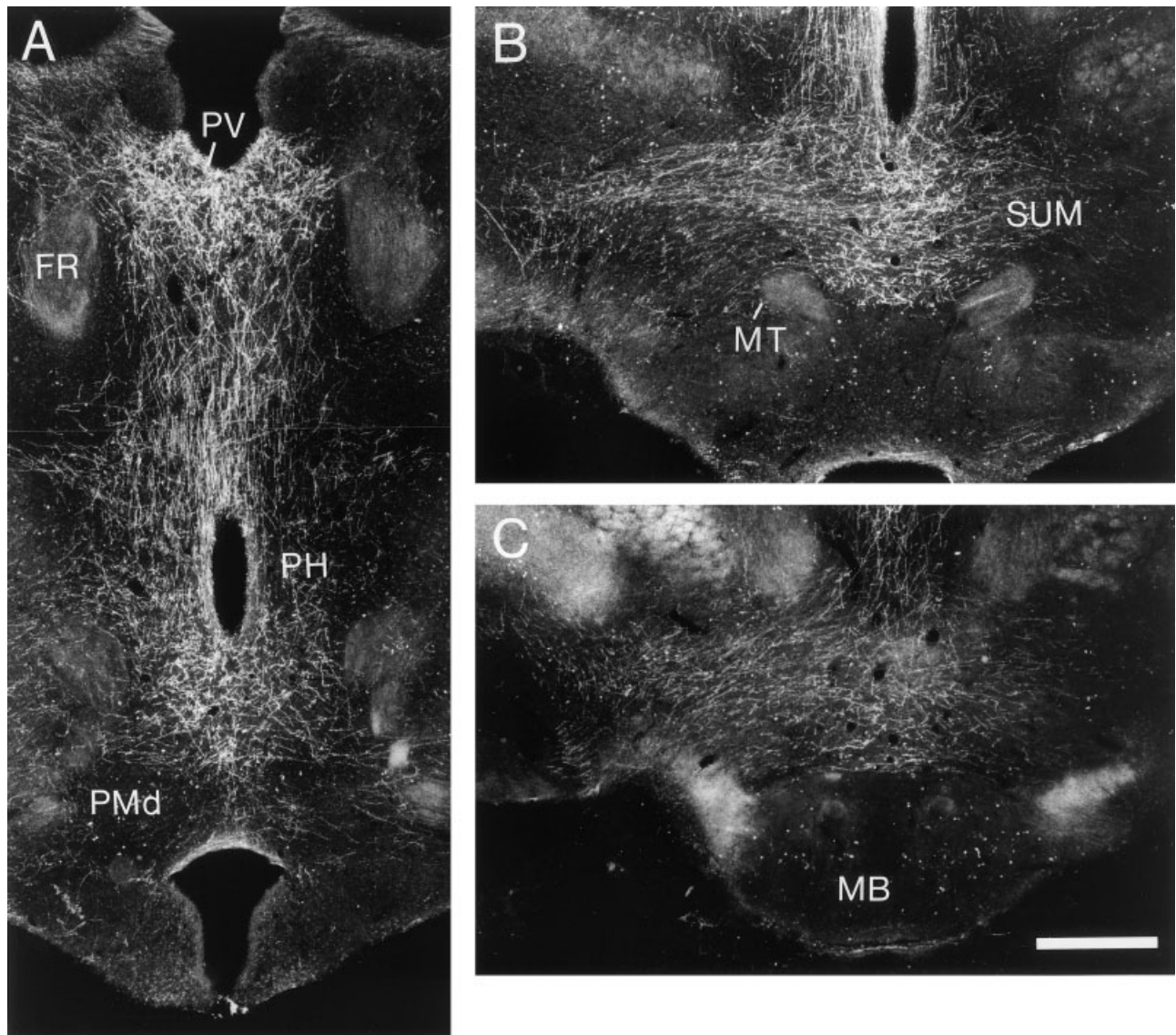


Fig. 5. Darkfield photomicrographs of transverse sections through the diencephalon showing patterns of labeling in caudal regions of the thalamus and hypothalamus. **A:** Pronounced labeling dorsoventrally along the midline in the paraventricular nucleus (PV) and intermedio-dorsal nucleus of thalamus (ventral to PV) and the posterior nucleus

(PH) of the hypothalamus. **B,C:** Labeling rostrally (**B**) and caudally (**C**) in the supramammillary nucleus (SUM), densest in the medial nucleus of SUM. Note absence of labeling in all parts of the mammillary complex (**A-C**) including the dorsal premammillary nucleus (PMd). Scale bar = 600  $\mu$ m.

parts of the olfactory forebrain and cortex, IL and PL distribute very differently throughout the brain. These differential patterns of projections undoubtedly reflect functional differences between IL and PL. The projections of IL are consistent with its involvement in visceromotor functions, functionally homologous to the orbitomedial PFC of primates (Neafsey, 1990; Barbas, 1995, 2000; Groenewegen and Uylings, 2000), whereas those of PL are consistent with a role in cognitive processes, functionally homologous to the dorsolateral prefrontal cortex of primates (Kolb, 1984; Goldman-Rakic, 1987, 1995; Groenewegen and Uylings, 2000).

#### Projections of the infralimbic cortex

The primary targets of IL fibers were: 1) the medial prefrontal (FPm, AC, PL, IL), orbital (mainly MO), insular, and entorhinal cortices; 2) the anterior piriform cortex, dorsal and ventral tania tecta, and anterior olfactory nucleus of the olfactory forebrain; 3) LPO, lateral aspects of MPO, SI, BST, LS, DBh, and endopiriform nucleus of the basal forebrain; 4) the medial, basomedial, cortical and central nuclei of the amygdala; 5) the PT, PV, MD, IMD, IAM, CEM, and RE of the thalamus; 6) the dorso-medial, lateral, perifornical, posterior, and supramammillary nuclei of the hypothalamus; and 7) the SNc, PAG, PB, and NTS of the brainstem (Table I, Fig. 12A).

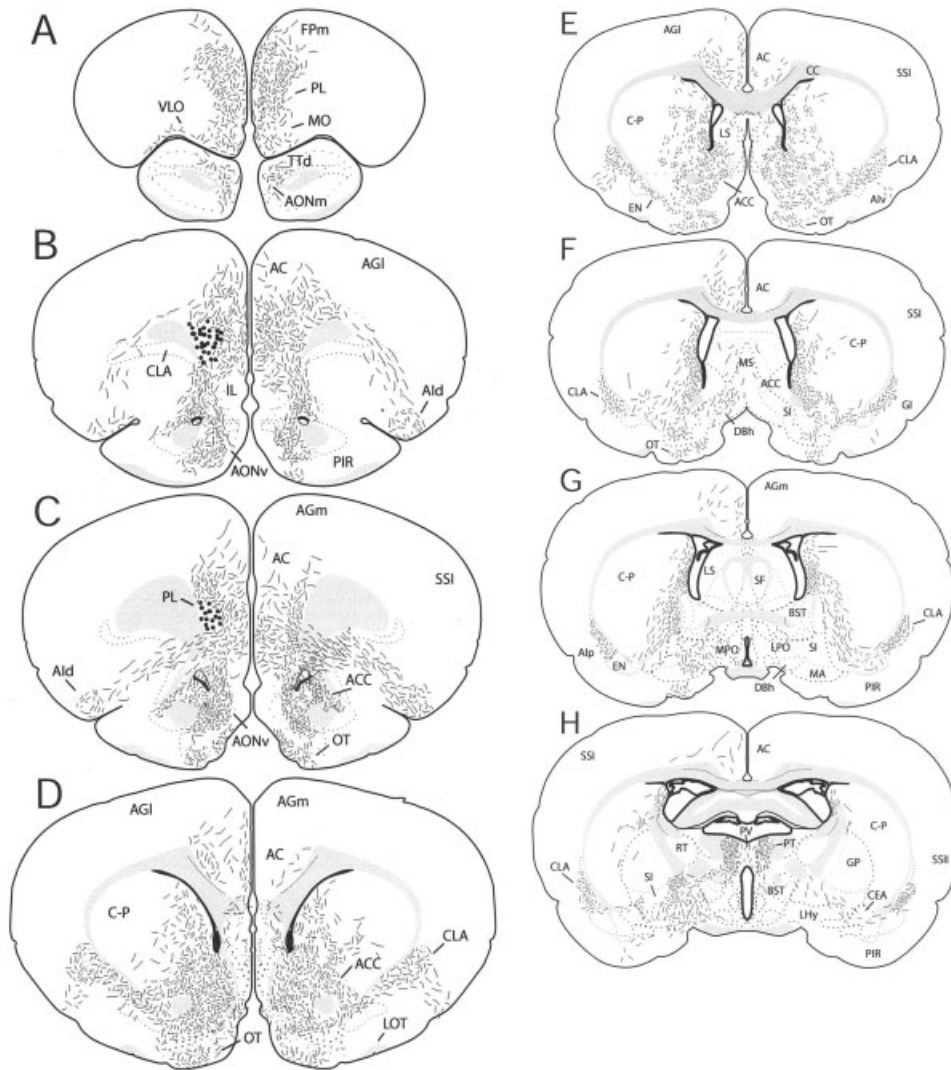


Fig. 6. Schematic representation of labeling present in selected sections through the forebrain and rostral brainstem (A-P) produced by a PHA-L injection (dots in B,C) in the prelimbic cortex (case 668). Sections modified from the rat atlas of Swanson (1998). For abbreviations, see list. (Figure 6 continued p. 44).

### Projections of the prelimbic cortex

The main targets of PL fibers were: 1) Fpm, IL, AC, MO, AI (dorsal and ventral divisions), and EC of the cortex; 2) the anterior PIR, AONm,v, and TTd of the olfactory forebrain; 3) medial C-P, the nucleus accumbens (shell and core), OT, and CLA of the basal forebrain; 4) PT, PV, AM, IAM, CEM, MD-IMD, and RE of the midline thalamus; 5) the central and basolateral nuclei of the amygdala; and 6) VTA, SNc, PAG, suprallemniscal nucleus (B9), DR, and MR of the brainstem (Table I, Fig. 12B).

### Common IL and PL projections

Despite largely separate patterns of projections, IL and PL distribute commonly to some sites, mainly to the midline/medial thalamus. Both IL and PL project heavily (and bilaterally) to the paratenial, paraventricular, MD/

IMD, IAM, CEM, and nucleus reuniens of the midline thalamus. In addition, IL and PL project commonly to the anterior PIR, AONm,v, and dorsal and ventral tania tecta of the olfactory forebrain, and to parts of the orbitomedial, insular, and entorhinal cortices. PL distributes much more heavily than IL to the insular cortex.

### IL and PL projections: comparisons with previous studies

#### mPFC and adjacent regions of the prefrontal cortex

We showed that IL and PL distribute significantly to other subdivisions of the orbitomedial PFC; that is, densely to IL, PL, and AC and moderately to AGm and parts of the orbital cortex (MO, VO, and VLO).

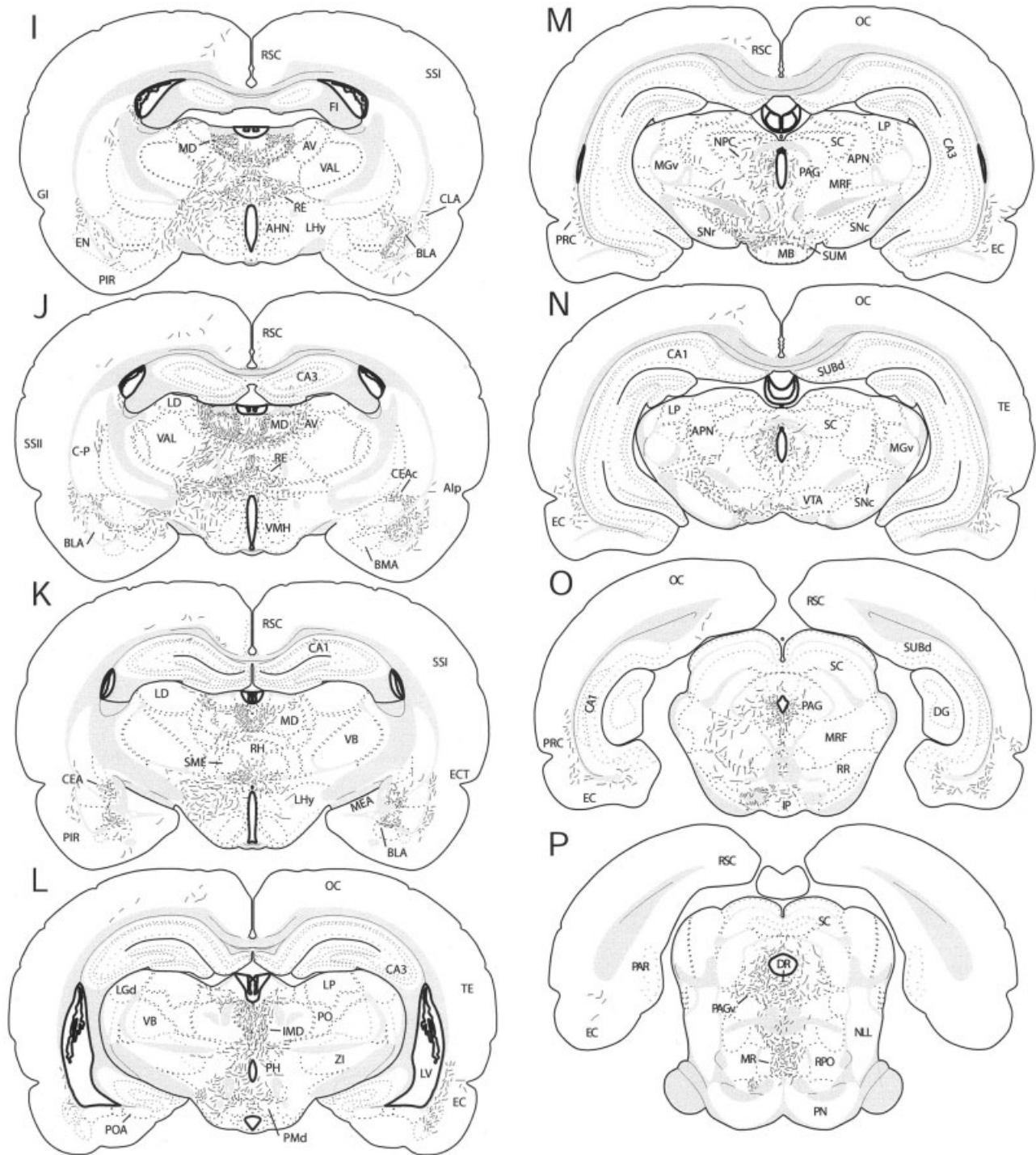


Figure 6 (Continued).

With few exceptions, previous studies have similarly demonstrated pronounced IL/PL projections to neighboring regions of the orbitomedial PFC. For instance, Takagishi and Chiba (1991) reported that IL fibers distribute widely throughout the mPFC; that is, to the medial precentral, PL, and dorsal peduncular cortices, as well as to rostral pole of VO and VLO. Hurley et al. (1991) demonstrated comparable results for IL, and

further noted that “control” injections in PL resulted in “extensive projections to all cortical areas located along the medial surface of the frontal lobe including layers I, II, III, and V of the medial orbital cortex, the tania tecta, the dorsal peduncular cortex, the ILC, and the anterior cingulate cortex.” Consistent with this, Sesack et al. (1989) found that PL fibers distribute to several regions adjacent to PL, including the rostrocaudal ex-

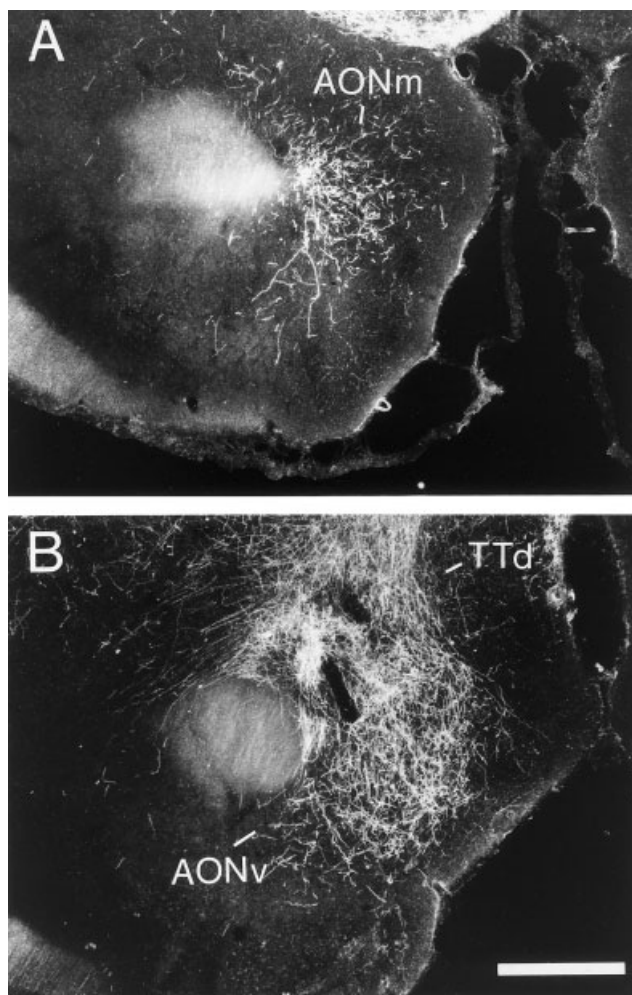


Fig. 7. Darkfield photomicrographs of transverse sections through rostral forebrain showing patterns of labeling in the anterior olfactory complex produced by an injection in the prelimbic cortex (case 668). Note pronounced labeling in the anterior medial olfactory nucleus (AONm), rostrally (A) and the dorsal tania tecta (TTd) and the anterior ventral olfactory nucleus (AONv), caudally (B). Scale bar = 600  $\mu$ m.

tent of the prelimbic and dorsal anterior cingulate cortices as well as to the medial precentral and infralimbic cortices. In contrast to the foregoing, Fisk and Wyss (1999) recently described fairly limited interconnections among subdivisions of the mPFC. It appears, however, that the injections of Fisk and Wyss (1999) were quite small, possibly resulting in a more restricted distribution of IL and PL fibers than shown in previous reports.

### Insular cortex (INC)

We showed that IL and PL project very differently to the INC. PL distributes much more heavily than IL to INC, and PL fibers are mainly directed to the rostral agranular insular cortex (dorsal and ventral divisions), and IL fibers to the posterior agranular INC.

In accord with the present findings, Hurley et al. (1991) reported that the IL projection to INC was a

relatively minor pathway, and remarked, in fact, that a reexamination of their earlier work (Saper, 1982a) revealed that mPFC cells retrogradely labeled from INC were "actually just beyond the border of IL, in the prelimbic cortex." A comparison of IL and PL projections in cats (Room et al., 1985) demonstrated considerably stronger PL than IL projections to INC, and further showed that PL fibers selectively target the rostral agranular INC. PL also distributes fairly selectively to AId in rats (Beckstead, 1979; Sesack et al., 1989). Finally, Shi and Cassell (1998) recently demonstrated that the agranular INC distributes to PL and the posterior INC to IL, indicating topographically organized reciprocal projections between IL/PL and INC.

### Clastrum (CLA) and endopiriform nucleus (EN)

We showed that IL projects to the endopiriform nucleus and PL to the claustrum of the claustrum/endopiriform complex. The claustrum consists of two main zones—the dorsal (or insular) claustrum and the ventral (or piriform) claustrum, also termed the endopiriform nucleus. It is well documented that CLA/EN is reciprocally linked to virtually all areas of the cortex (Markowitsch et al., 1984; Sloniewski et al., 1986; Sherk, 1988; Witter et al., 1988; Kowianowski et al., 1998; Majak et al., 2000; Zhang et al., 2001).

Although a few reports have described projections from the PFC to parts of the claustrum (Markowitsch et al., 1984; Witter et al., 1988; Majak et al., 2000), to our knowledge none have examined possible differential IL and PL projections to CLA/EN. Despite this, an early anatomical analysis of IL (Hurley et al., 1991) demonstrated terminal IL labeling in EN, but interestingly, none in CLA (see their fig. 3A, p. 254), while an examination of PL (Sesack et al., 1989) showed the reverse: PL projections to CLA but not to EN (see their fig. 4, p. 220). In accord with the foregoing, Levesque and Parent (1998) recently showed that a subpopulation of PL cells project, via collaterals, to the claustrum and striatum, while Zhang et al. (2001) demonstrated that injections of retrograde tracers in the anterior CLA produced significant labeling in PL but virtually none in IL.

### Nucleus accumbens (ACC)

We showed that IL and PL project very differently to ACC. PL fibers distribute massively throughout the core and shell regions of ACC. By contrast, IL fibers project fairly selectively to the caudo-medial sector (shell) of ACC.

PFC projections to ACC have been well documented (Beckstead et al., 1979; Newman and Winans, 1980; Groenewegen et al., 1982; McGeorge and Faull, 1989; Sesack et al., 1989; Hurley et al., 1991; Berendse et al., 1992; Brog et al., 1993; Phillipson and Griffiths, 1985;

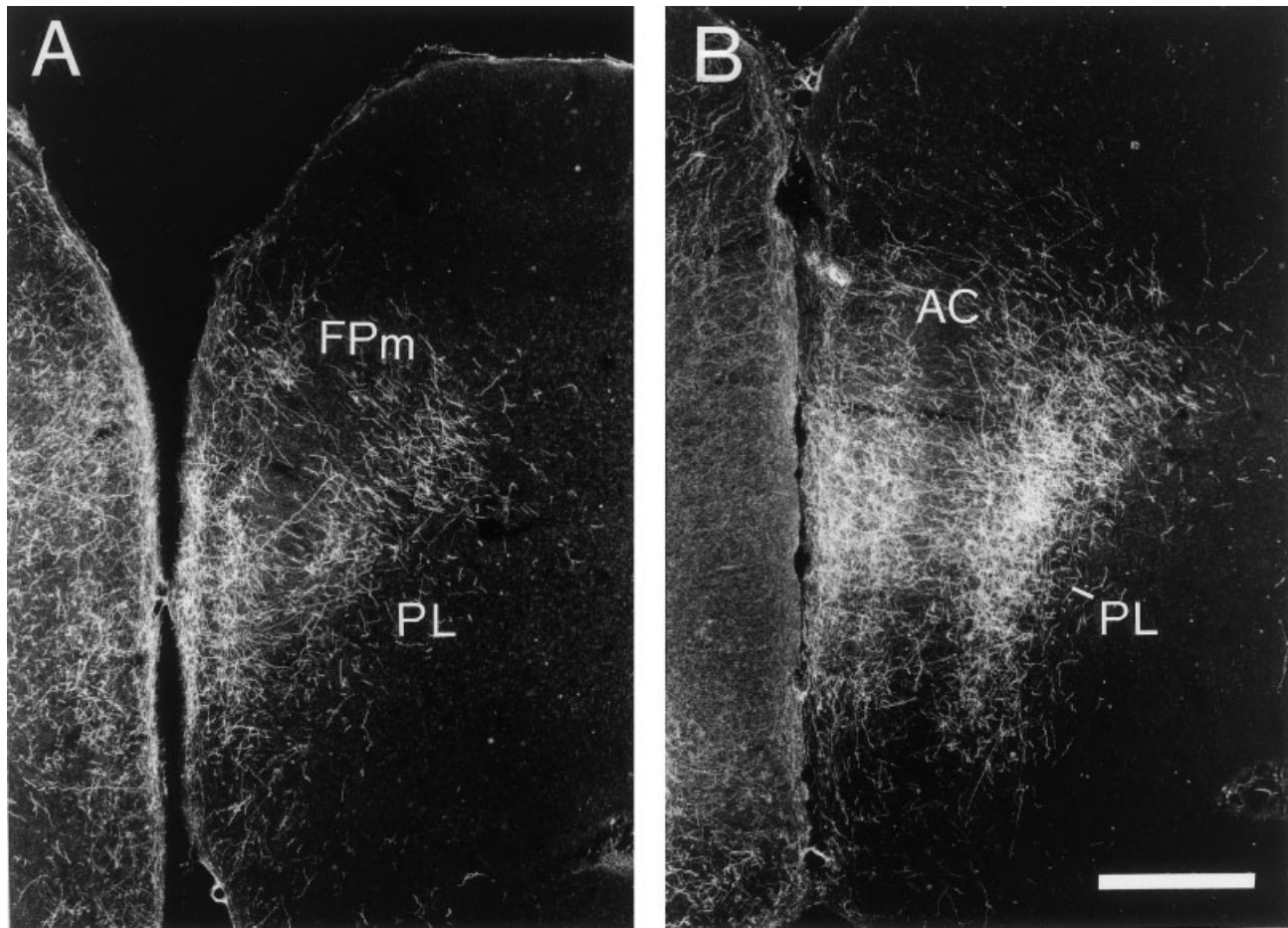


Fig. 8. Darkfield photomicrographs of transverse sections through the rostral forebrain depicting labeling contralaterally in the medial prefrontal cortex produced by an injection in the prelimbic cortex (case 668). Note pronounced labeling in all layers of the contralateral prelimbic cortex (PL), most heavily concentrated in layers 1/2 and 5/6, as well as significant labeling in the frontal polar (FPm) cortex (A) and the anterior cingulate (AC) cortex (B), dorsal to PL. Scale bar = 600  $\mu$ m.

Room et al., 1985; Wright and Groenewegen, 1995, 1996; Montaron et al., 1996; Gorelova and Yang, 1997; Ding et al., 2001; French and Totterdell, 2002).

In accord with present findings, mPFC projections to ACC appear to primarily originate from PL of PFC (Beckstead et al., 1979; Sesack et al., 1989; Berendse et al., 1992; Brog et al., 1993; Montaron et al., 1996). For instance, Sesack et al. (1989) described a pattern of PL projections to ACC virtually identical to that shown here; that is, pronounced labeling throughout ACC, excluding the caudal shell of ACC. In like manner, a comprehensive analysis of PFC-striatal projections in rats (Berendse et al., 1992) showed that IL fibers mainly target the medial shell of ACC, whereas PL fibers distribute throughout extent of ACC, terminating more heavily in the core than shell of ACC. The PL-ACC projections described by Berendse et al. (1992) were, however, less robust than shown by others (Beckstead et al., 1979; Sesack et al., 1989, present results). Differences probably involve relative locations of injections across studies, as suggested by Sesack et al.'s

(1989) demonstration of marked variations in the density of labeling in ACC with injections in different parts of PL.

#### **BST and other structures of the medial basal forebrain**

We found that IL and PL project very differently to the basal forebrain. IL distributes significantly to the anterior part of the lateral septum, DBh, BST, SI, lateral MPO and LPO, whereas PL projects sparingly to each of these sites.

Consistent with this, an early comparison of IL/PL projections in cats (Room et al., 1985) demonstrated dense IL, but minimal PL, projections to the rostral septum, medial, and lateral preoptic area, diagonal band nuclei, BST, and SI. In like manner in rats, Takagishi and Chiba (1991) showed that IL distributes heavily to medial aspects of the lateral septum, the diagonal band nuclei, LPO, BST, and SI, while Hurley et al. (1991) described virtually the same, drawing

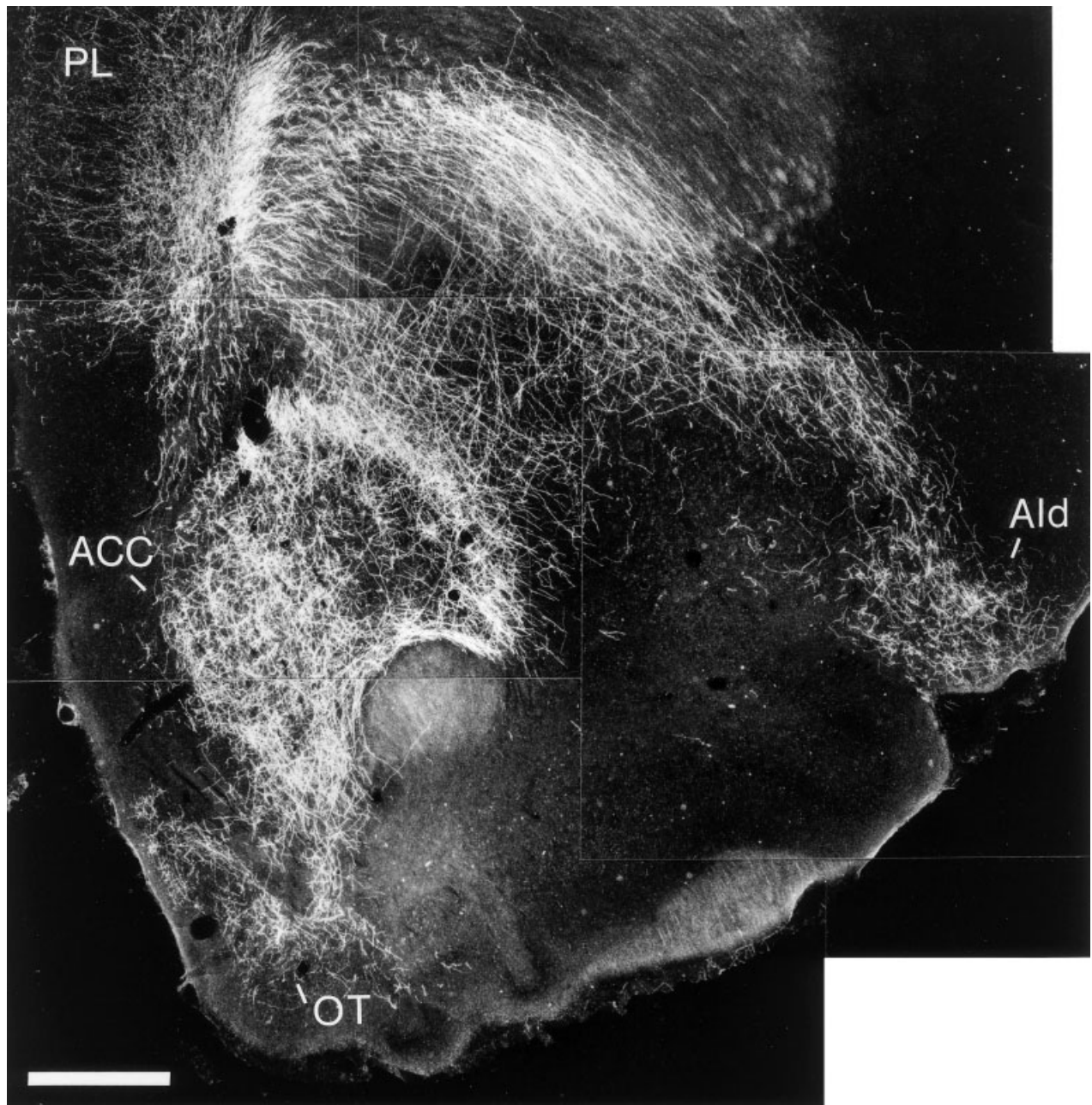


Fig. 9. Darkfield photomicrograph of a transverse section through the rostral forebrain showing labeling contralaterally in the forebrain produced by an injection in the prelimbic cortex (case 668). Note dense collection of ventrolaterally oriented labeled fibers terminally bound

for the dorsal agranular insular cortex (Aid). Note also massive labeling throughout the extent (shell and core) of the anterior pole of nucleus accumbens (ACC) as well as significant labeling in the ventrally adjacent olfactory tubercle (OT). Scale bar = 600  $\mu$ m.

particular attention to strong IL projections to MPO and BST.

Unlike IL, Sesack et al. (1989) showed that injections of PHA-L into various regions of PL produced an essential absence of labeling within the basal forebrain. For instance, they described a minor PL input to the medial septum, DBv, ventral pallidum, and SI and noted that only "sparse fibers-of-passage were visible in the bed nucleus of the stria terminalis."

Finally, injections of retrograde tracers in BST (Hurley et al., 1991), SI (Russchen et al., 1985; Grove, 1988a), and the horizontal and vertical limbs of the diagonal band (Carnes et al., 1990) have been shown to produce significant cell labeling IL but virtually none in PL.

#### Amygdala

We showed that IL and PL project very differently to the amygdala. IL fibers distribute widely through-





Fig. 10. Darkfield photomicrograph of a transverse section through the rostral forebrain depicting labeling contralaterally in the forebrain produced by an injection in the prelimbic cortex (case 668). Note dense terminal labeling in the claustrum (CLA), dorsal agranular insular cortex (AId), ventromedial striatum (C-P), and the shell and core regions of nucleus accumbens (ACC). Scale bar = 600  $\mu$ m.

out the anterior two-thirds of the amygdala, mainly to rostral MEA, the capsular and medial subdivisions of CEA, and to the basomedial nucleus. By contrast, PL fibers selectively target the central nucleus (capsular portion) and the basolateral nucleus of the amygdala.

Hurley et al. (1991) described moderately dense IL projections to the central (medial aspects), medial, basomedial and anterior cortical nuclei of the amygdala, and a virtual absence of projections to the lateral and basolateral nuclei, while McDonald et al. (1996) re-

ported that IL fibers distribute to "all major portions of the amygdala." They noted particularly heavy IL projections to the lateral capsular portion of CEA, BMA, and medial part of the lateral nucleus (McDonald et al., 1996).

An early study in rats (Beckstead, 1979) demonstrated significant PL projections to the lateral and basolateral nuclei of amygdala and to the region surrounding, but not in, CEA (i.e., to capsular CEA), while one in cats (Room et al., 1985) showed that PL projections were "restricted to the basolateral and central

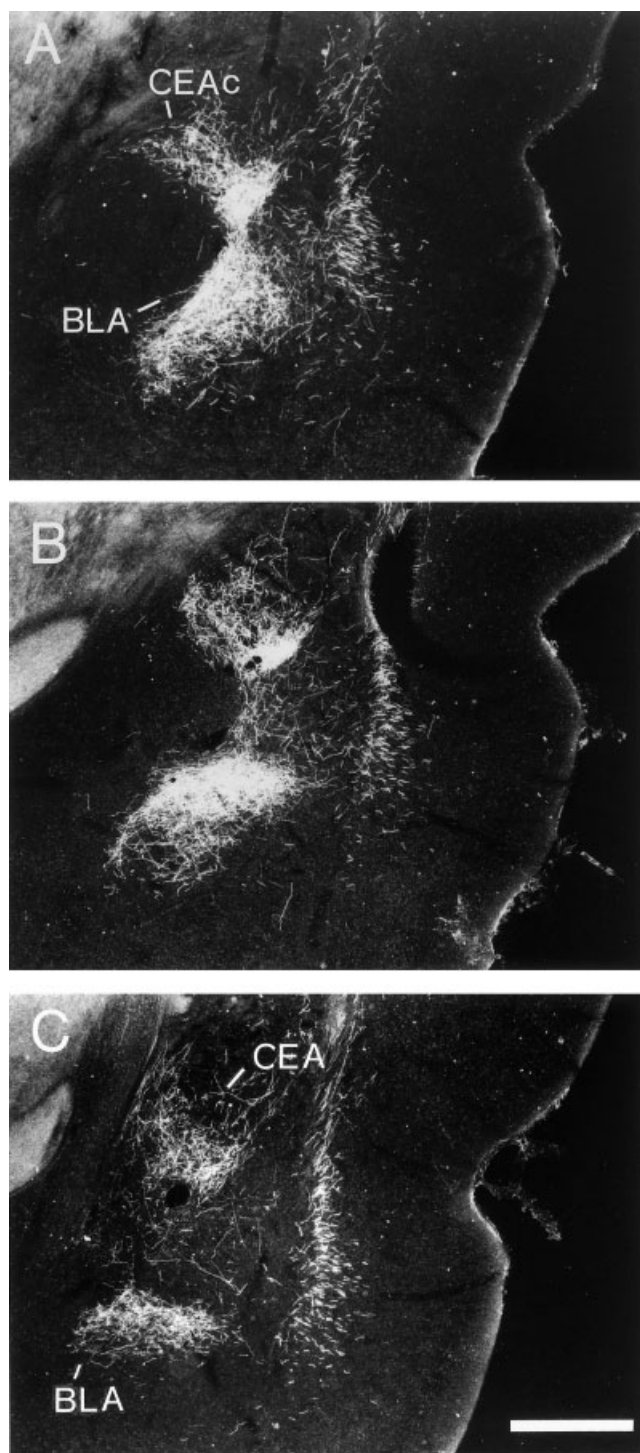


Fig. 11. Darkfield photomicrographs of transverse sections through the forebrain showing patterns of labeling contralaterally at three rostrocaudal (A–C) levels of the amygdala produced by an injection in the prelimbic cortex (case 668). Note dense labeling predominantly restricted to the capsular part of the central nucleus (CEAc) and the basolateral (BLA) nuclei of amygdala. Scale bar = 600  $\mu$ m.

nuclei.” More recently, Sesack et al. (1989) reported that PL fibers distribute selectively to the zone surrounding CEA (capsular CEA) and to the lateral, baso-

lateral, and intercalated nuclei of amygdala, while McDonald et al. (1996) demonstrated that PL targets the anterior amygdaloid area, medial/dorsomedial BLA, and the capsular (mainly lateral capsular) CEA.

In summary, previous findings support the present demonstration that IL distributes widely throughout the amygdala; by contrast, PL fibers primarily project to the capsular CEA and BLA, and less so to the anterior, lateral, and intercalated nuclei of amygdala.

### Thalamus

Unlike most other regions of the brain, we showed that IL and PL distribute commonly to the thalamus, predominantly to structures of the midline/medial thalamus. Both IL and PL project heavily to the paratenial (PT), paraventricular (PV), anteromedial (AM), interanteromedial (IAM), mediodorsal (MD), intermediodorsal (IMD), reuniens (RE), and central medial nuclei (CEM) of thalamus, and moderately to the parafascicular and rhomboid nucleus.

Our findings are consistent with previous anterograde analyses of IL and PL projections to the thalamus (Beckstead, 1979; Room et al., 1985; Sesack et al., 1989; Hurley et al., 1991; Takagishi and Chiba, 1991; Buchanan et al., 1994; Vertes, 2002), as well as with retrograde examinations of afferents to PT-PV (Chen and Su, 1990; Hurley et al., 1991; Risold et al., 1997), IMD-MD (Groenewegen, 1988; Cornwall and Phillipson, 1988; Hurley et al., 1991), RE (Herkenham, 1978; Hurley et al., 1991; Risold et al., 1997), and AM (Seki and Zyo, 1984).

### Hypothalamus

We showed that IL and PL project very differently to the hypothalamus. IL projects significantly to the dorsomedial hypothalamic nucleus/area, the lateral hypothalamus, perifornical region, posterior and supra-mammillary nuclei. By contrast, PL fibers mainly traverse the hypothalamus en route to the brainstem, distributing lightly in transit to PH, SUM, and parts of LH<sub>y</sub>.

Hurley et al. (1991) described significant IL projections to LH<sub>y</sub>, PF<sub>x</sub>, DMH, PH, and SUM of the hypothalamus, and further noted that “control” injections in PL produced relatively scant labeling in the hypothalamus, sparsely distributed to the lateral hypothalamus. In like manner, Room et al. (1985) showed for cats that IL distributes densely, PL lightly, to the septum, medial preoptic area, and dorsomedial and lateral hypothalamus. In slight contrast to the foregoing, Sesack et al. (1989) reported that a PHA-L injection in the rostroventral PL produced moderate labeling in LH<sub>y</sub>, SUM, and medial MB. They pointed out, however, that this injection spread to the underlying IL and medial orbital cortices, which could have contributed to the hypothalamic labeling observed with this case. Injec-

tions in other parts of PL resulted in an essential absence of labeling in the hypothalamus (Sesack et al., 1989). Consistent with these findings, we observed a similar dorsal-ventral gradient in PL projections to the hypothalamus from an essential absence of hypothalamic projections with dorsal injections to light (and in some cases) moderate hypothalamic labeling with ventral PL injections, bordering IL.

Finally, Floyd et al. (2001) recently demonstrated that the rostroventral IL/PL projects to the dorsal hypothalamic area, LHy, lateral PFx, and PH, while the caudoventral IL/PL projects to these sites as well as to the dorsolateral AHN, the dorsal hypothalamic nucleus and medial PFx.

### Brainstem

With some overlap, IL and PL largely distribute to separate sites in the brainstem. IL mainly targets SNc, dorsal aspects of IP, ventrolateral regions of the pontomesencephalic PAG, the medial and lateral parabrachial nuclei and NTS. PL primarily distributes to VTA, SN (pars compacta and reticulata), precommissural nucleus (PCO), the lateral and ventrolateral pontine PAG, the suprallemniscal nucleus (B9) (Vertes and Crane, 1997), and the dorsal and median raphe nuclei. PL distributes more heavily than IL to common targets: VTA, SNc, and ventrolateral PAG. PL fibers spread mediolaterally throughout SNc, whereas IL fibers predominantly terminated in the medial one-third of SNc.

Several early reports (Ross et al., 1981; Saper, 1982b; Terreberry and Neafsey, 1983, 1987; van der Kooy et al., 1984; Neafsey et al., 1986b; van Bockstaele et al., 1989; Moga et al., 1990a) showed that IL fibers strongly (and fairly selectively) target autonomic/visceral-related nuclei of the brainstem; specifically, the ventrolateral PAG, PB, Barrington's nucleus, NTS, and the rostral ventrolateral medulla. Hurley et al. (1991) confirmed these results, and further demonstrated IL projections to the nucleus ambiguus (NA) and to the dorsal motor nucleus of the vagus (DMV). In partial contrast with the foregoing, we demonstrated moderate IL projections to "autonomic-related" nuclei of the upper brainstem (e.g., parabrachial nucleus), and sparse projections to those of the lower brainstem including NA, NTS, and DMV.

By comparison with IL, PL fibers distribute more widely throughout the pons and midbrain, and with the exception of PAG, largely avoid autonomic nuclei of the brainstem (Beckstead, 1979; Sesack et al., 1989; Floyd et al., 2000). In general accord with present findings, Beckstead (1979) described prominent PL projections to SNc and the adjoining VTA and significant but less dense ones to DR and MR, while Sesack et al. (1989) traced PL fibers to SNc, VTA, IP, dorsolateral PAG, SLN (B9), DR, and MR.

Finally, other (mainly retrograde) reports have documented PL projections to VTA (Sesack and Pickel, 1992; Au-Young et al., 1999; Carr and Sesack, 2000), PCO (Canteras and Goto, 1999), DR (Peyron et al., 1998; Hajos et al., 1998; Varga et al., 2001), MR (Behzadi et al., 1990), and PAG (Beitz, 1982, Mantyh, 1982, Hardy, 1986; Neafsey et al., 1986b; Terreberry and Neafsey, 1987; Shipley et al., 1991).

## Overview of IL and PL projections and functional considerations

### IL: visceromotor circuitry

It is well recognized that IL modulates visceral/autonomic activity. A number of early reports (Smith, 1945; Wall and Davis, 1951; Delgado, 1961) as well as recent ones (Terreberry and Neafsey, 1983; Burns and Wyss, 1985; Hurley-Gius and Neafsey, 1986; Verberne et al., 1987; Hardy and Holmes, 1988, Neafsey, 1990; Frysztak and Neafsey, 1991, 1994) have shown that IL significantly affects various visceral functions including heart rate, blood pressure, respiration, and gastrointestinal activity. It is equally well demonstrated (Cechetto and Saper, 1990; Neafsey, 1990; Hurley et al., 1991; Takagishi and Chiba, 1991; Buchanan and Powell, 1993; Verberne and Owens, 1998) that IL projects to forebrain and brainstem sites controlling autonomic/visceromotor activity (see Fig. 12A).

Further, it has been shown that most of the major forebrain targets of IL fibers project to, and influence, autonomic nuclei of the brainstem (Saper et al., 1976, 1979; Hopkins and Holstege, 1978; Schwaber et al., 1982; Veening et al., 1984; Moga and Gray, 1985; Grove, 1988b; Moga et al., 1989, 1990a,b; Loewy, 1991; Rizvi et al., 1991, 1992, 1996; Allen and Cechetto, 1992; Vertes and Crane, 1996; Petrovich and Swanson, 1997; Murphy et al., 1999; Floyd et al., 2001), indicating direct as well as indirect IL actions on a network of interconnected nuclei subserving autonomic/visceral functions. IL is viewed as a "visceral motor cortex" (Hurley-Guis and Neafsey, 1986; Neafsey, 1990).

Related to the involvement of IL is visceral motor control, Milad and Quirk (2002) recently demonstrated the important findings that cells of the infralimbic cortex, but not those of the adjacent PL and medial orbital cortices, fired selectively during the extinction phase of fear conditioning, and were thought to mediate learned fear extinction. The authors proposed that the effect involves the suppressive action of IL on the central nucleus of the amygdala and a consequent dampening of autonomic/visceral centers contributing in fear responses (Milad and Quirk, 2002).

### PL: "limbic-cognitive" circuitry

By contrast with IL, recent evidence suggests that PL serves a direct role in limbic/cognitive functions, homologous to the dorsolateral prefrontal cortex of pri-

TABLE I. Density of labeling in nuclei of the brainstem and forebrain produced by PHA-L injections in the infralimbic and prelimbic cortices\*

Structures	Labeling		Structures	Labeling	
	IL	PL		IL	PL
Telencephalon			substantia innominata	+++	+
cortex			tania tecta		
cingulate	+++	+++	dorsal	++	++
ectorhinal	+	--	ventral	+	--
entorhinal	++	++	ventral pallidum	+	--
frontal polar			Diencephalon		
medial part	+++	+++	Thalamus		
lateral part	--	--	anterodorsal n.	--	--
infralimbic	+++	+++	anteromedial n.	+	++
insular			anteroventral n.	--	--
dorsal agranular	+	+++	central lateral n.	--	+
ventral agranular	++	+++	central medial n.	++	++
posterior agranular	+	--	interanteromedial	++	+++
dysgranular	--	--	intermediodorsal n.	+++	+++
granular	--	--	lateral geniculate n.	--	--
lateral agranular (motor)	--	--	lateral habenula	+	+
medial agranular (motor)	+	+	laterodorsal n.	+	+
occipital	--	--	lateroposterior n.	+	+
orbital			medial geniculate n.	--	--
lateral part	+	+	medial habenula	--	--
medial part	+++	+++	mediodorsal n.		
ventral part	++	+	medial division	+++	+++
ventrolateral part	+	+	central division	++	++
perirhinal	+	++	lateral division	+	+++
piriform			paracentral n.	--	--
anterior part	--	+	parafascicular n.	+	+
posterior part	++	--	paratentorial n.	+++	+++
prelimbic	+++	+++	paraventricular n.		
retrosplenial	+	+	anterior part	+++	+++
somatosensory I	--	--	posterior part	+++	+++
somatosensory II	--	--	posterior n.	--	--
temporal	--	--	reticular n.	--	--
accumbens n.			reuniens n.	+++	+++
shell	+	+++	rhomboid n.	++	+
core	+	+++	submedial n.	--	--
amygdala			ventral anterior-lateral n.	--	--
anterior area	++	--	ventral basal complex	--	--
basolateral	+	+++	Hypothalamus		
basomedial	+++	+	anterior n.	++	--
central			dorsal hypothalamic area	++	+
capsular part	++	+++	dorsomedial n.	+++	+
medial part	+++	++	lateral n.	+++	++
cortical			mammillary bodies	+	--
anterior part	++	--	paraventricular n.	--	--
posterior part	+	--	perifornical area	+++	++
medial	+++	--	posterior n.	+++	+
lateral	+	+	premamillary n.		
posterior	+	--	dorsal	--	--
anterior olfactory nucleus			ventral	+	--
medial part	+++	++	supramammillary n.	++	++
ventral part	+++	+++	ventromedial n.	--	--
bed n. of stria terminalis	+++	--	Subthalamus		
caudate-putamen	++	++	fields of Forel	+	--
claustrum	--	+++	zona incerta	+	--
diagonal band n.			Brainstem		
horizontal limb	+++	+	anterior pretectal n.	--	--
vertical limb	++	--	Barrington's n.	+	+
endopiriform n.	+++	--	cuneiform n.	--	+
globus pallidus	--	--	dorsal motor n. vagus	+	--
hippocampal formation			dorsal raphe n.	+	+++
Ammon's horn	--	--	dorsal tegmental n.	--	--
dentate gyrus	--	--	interpeduncular n.	++	+
subiculum	--	--	laterodorsal tegmental n.	+	+
lateral septum			locus coeruleus	+	--
dorsal n.	++	--	mesencephalic reticular formation	+	+
intermediate n.	+	--	n. ambiguus	--	--
ventral n.	+++	+	n. incertus	+	++
lateral preoptic area	+++	+	n. gigantocellularis	--	+
magnocellular preoptic n.	+	+	n. pons	--	--
medial preoptic area	+++	+	n. pontis caudalis	--	--
median preoptic n.	++	--	n. pontis oralis	--	--
medial septal n.	+	--	n. posterior commissure		
olfactory tubercle	++	+++	n. solitary tract	+	--
septofimbrial n.	--	--	parabrachial n.		
septohippocampal n.	++	--	medial part	++	--

TABLE I (CONTINUED).

Structures	Labeling	
	IL	PL
lateral part	++	--
pedunclopontine tegmental n.	+	+
periaqueductal gray, midbrain	+++	+++
periaqueductal gray, pons	+	+++
peripeduncular n.	--	+
reticular tegmental n. pons	--	--
retrotrubral area	--	+
rostromedial medulla	--	--
pars compacta	+	+++
pars reticulata	--	++
surpalemniscal n. (B9)	--	+
superior colliculus	--	--
ventral tegmental area	++	++
ventral tegmental n.	--	--

\*+, light labeling; ++, moderate labeling, +++, dense labeling; --, absence of labeling; n, nucleus; PHA-L, *Phaseolus vulgaris*-leucoagglutinin; for other abbreviations, see list.

mates (Kolb, 1984; Barbas, 2000; Ongur and Price, 2000). The dorsolateral PFC of primates serves a well-recognized role in higher order processes, including decision-making, goal-directed behavior, and working memory (WM) (Goldman-Rakic, 1987, 1994; Fuster, 1989; Petrides, 1995, 1998). The function most commonly associated with the prefrontal cortex, and the one most extensively examined, is working memory; that is, the temporary storage and utilization of information over short delays (Goldman-Rakic, 1987, 1995).

An accumulating body of evidence indicates that the prefrontal cortex of rats is similarly involved in tasks requiring the maintenance of information over time including delayed alternation (Larsen and Divac, 1978; Silva et al., 1986; van Haaren et al., 1988; Brito and Brito, 1990; Bubser and Schmidt, 1990; Kesner et al., 1996; Delatour and Gisquet-Verrier, 1996, 1999) and delayed matching and nonmatching to sample tasks (Kolb et al., 1994; Granon et al., 1994; Broersen et al., 1995; Seamans et al., 1995; Harrison and Mair, 1996; Shaw and Aggleton, 1993; Young et al., 1996; Porter and Mair, 1997). Evidence further suggests that PL is the critical mPFC region involved in delayed responding; that is, lesions restricted to ventral mPFC (or PL) have been shown to produce the same disruptive effects on delayed response tasks as lesions of the entire medial wall of the mPFC (Bruto and Brito, 1990; Seamans et al., 1995; Delatour and Gisquet-Verrier, 1996, 1999, 2000; Floresco et al., 1997; Ragozzino et al., 1998). For instance, Phillips and co-workers (Seamans et al., 1995) initially demonstrated that bilateral inactivation of PL, but not of the dorsally adjacent anterior cingulate cortex, produced severe deficits in the delayed version of an eight arm maze task, and subsequently showed that these same deficits were produced by disconnecting the hippocampus from PL (Floresco et al., 1997).

As with IL projections and visceromotor activity, PL projections support its involvement in cognitive functions. As shown (Fig. 12B), PL distributes to a rela-

tively restricted number of sites and largely those known to affect cognition—or limbic influences on cognition. These include the agranular insular cortex, the claustrum, ACC (and extended ventral striatum), basolateral amygdala, the paraventricular, RE and MD of thalamus, VTA/SNc, and raphe nuclei of the midbrain (SLN, DR, and MR).

### PL-striatal-thalamocortical circuitry

Similar to sensorimotor regions of cortex (Alexander et al., 1986, 1990; Gerfen, 1992; Gerfen and Wilson, 1996; Strick et al., 1994), the prefrontal cortex forms reentrant “loops” with the basal ganglia (BG) and thalamus; that is, parallel, functionally segregated, cortical-BG-thalamocortical circuits (Groenewegen et al., 1990, 1999).

In an early report in cats, Room et al. (1985) described pronounced projections from PL to the ACC, and further noted that the PL-ACC projection was the first leg of a cortical loop from PL; that is, according to them, a loop “from the prelimbic area via the ventral striatum, ventral pallidum, and the mediodorsal nucleus back to the prelimbic area.” As discussed below, several subsequent studies have provided additional details on this system of connections that has been referred to as the “PL circuit” (Groenewegen et al., 1990).

The ACC is the major point of convergence of inputs from various structures comprising the “PL circuit”; that is, in addition to PL, ACC receives afferents from the insular cortex, basal nucleus of amygdala, VTA, midline thalamus, ventral pallidum, and hippocampus (Groenewegen et al., 1990). The output of ACC is predominantly directed to the ventral pallidum (VP) and SNr (Groenewegen and Russchen, 1984; Zahm and Heimer, 1990; Heimer et al., 1991; Deniau et al., 1994; Zahm et al., 1996; Maurice et al., 1997; O'Donnell et al., 1997; Usuda et al., 1998; Dallvechia-Adams et al., 2001) which, in turn, project to parts of the medial/midline thalamus (mainly MD) that give rise to projections to PL, thus completing the PL-ventral striatopallidal-thalamocortical circuit (Haber et al., 1985; Groenewegen, 1988; Zahm, 1989; Ray and Price, 1992; Ray et al., 1992; Groenewegen et al., 1993, 1999; Miyamoto and Jinnai, 1994; Kuroda et al., 1995; Maurice et al., 1997; O'Donnell et al., 1997).

Two parallel (but segregated) PL-ventral BG-thalamic circuits have recently been identified: one originating from the ventral PL targeting the shell of ACC, and the other from the dorsal PL feeding the core of ACC (O'Donnell et al., 1997; Groenewegen et al., 1999). The ventral PL circuit, then, involves: ventral PL > ACC shell > VPM > medial subdivision of MD (MDm) > PL; and the dorsal PL circuit involves: dorsal PL > ACC core > VPI and/or dorsomedial SNr > central nucleus of MD/ventromedial nucleus of thala-

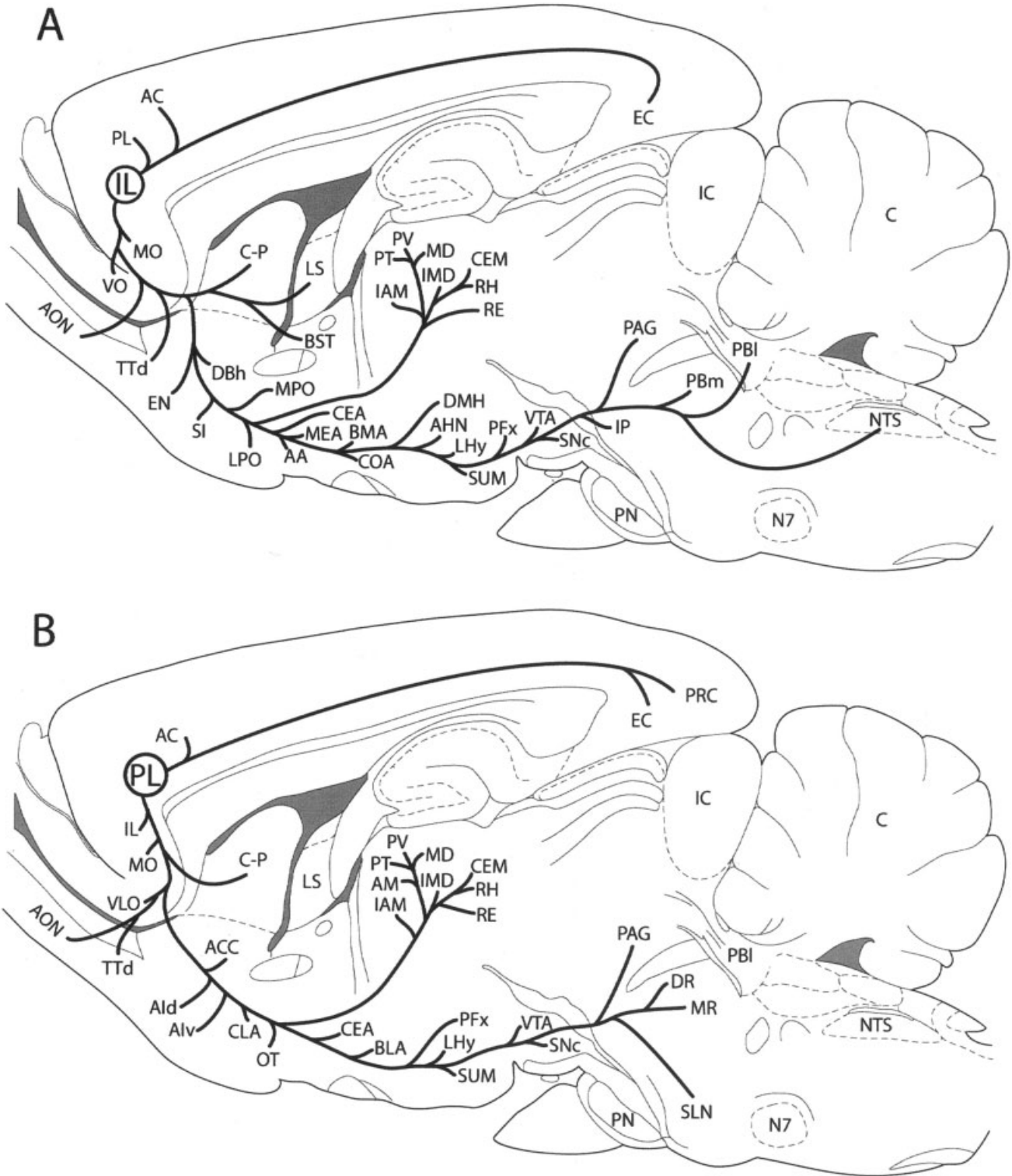


Fig. 12. Schematic sagittal sections summarizing the main projection sites of the infralimbic (A) and prelimbic (B) cortices. Note that IL projections are much more widespread than PL projections, particularly to the basal forebrain, amygdala, and hypothalamus. Sections are modified from the rat atlas of Paxinos and Watson (1998). For illustrative purposes, several sagittal planes are collapsed onto single sagittal sections. For abbreviations, see list.

mus > PL (O'Donnell et al., 1997; Groenewegen et al., 1999). As described (see Results), we carefully examined PL projections to the ACC but were not able to confirm selective dorsal PL projections to the core of ACC and ventral PL projections to the shell of ACC. By contrast, we observed considerable overlap in dorsal and ventral PL projections to the core and shell of ACC with only a slight tendency of dorsal PL to distribute more heavily to the core and the ventral PL more strongly to the shell. This difference in degree may not, however, negate the fact that there are segregated PL circuits—to the striatum and to other parts of the brain.

Finally, a direct role for the “PL circuit” in cognition gains support from recent demonstrations that manipulations of nuclei of the circuit (like those of PL itself) affect delay response tasks—or working memory (WM). For instance, lesions/disruption of ACC (Floresco et al., 1999), VP (Kalivas et al., 2001), and MD (Harrison and Mair, 1996; Floresco et al., 1999; Romanides et al., 1999; Kalivas et al., 2001) have been shown to alter tasks requiring working memory, but not those without a WM component.

#### Other “limbic” structures connecting with the PL circuit

Groenewegen et al. (1990) initially reported that the PL circuit has significant ties with other parts of the limbic system, most notably, the paraventricular nucleus of thalamus (PV) and the basolateral nucleus of amygdala (BLA). This has been substantiated by the demonstration that: 1) PV and BLA reciprocally connect with PL (Krettek and Price, 1977; Macchi et al., 1978; Beckstead, 1979; Room et al., 1985; McDonald, 1987, 1991a; Cassell et al., 1989; Sesack et al., 1989; Kita and Kitai, 1990; Berendse and Groenewegen, 1991; Shinonaga et al., 1994; Moga et al., 1995; Bacon et al., 1996; McDonald et al., 1996; Vertes, 2002); 2) PV and BLA distribute heavily to ACC (Groenewegen et al., 1980; Russchen and Price, 1984; Phillipson and Griffiths, 1985; Berendse and Groenewegen, 1990; McDonald, 1991b; Brog et al., 1993; Shinonaga et al., 1994; Moga et al., 1995; Wright and Groenewegen, 1995; Wright et al., 1996; Mulder et al., 1998); and 3) BLA afferents to thalamus selectively target midline nuclei of the thalamus (Krettek and Price, 1974, 1977; McDonald, 1987; Kuroda and Price, 1991; Ray and Price, 1992).

We confirmed pronounced PL projections to PV and BLA, and further showed that PL distributes strongly to several other structures that, in light of the notion of a “PL circuit,” might be considered part of an extended PL circuitry. They primarily include the agranular insular cortex, the claustrum, the nucleus reuniens of thalamus, SNc/VTA, and raphe nuclei (MR, DR, SLN) of the brainstem (Fig. 12B).

#### Integration of IL and PL circuitry

As described, IL and PL project very differently throughout the brain (Table I, Fig. 12). IL mainly distributes to autonomic/visceral-related sites, supporting its role in visceromotor activity, whereas PL primarily projects to limbic sites that reportedly affect cognition.

It is obviously the case, however, that the complex goal-directed behaviors entail an integration of visceral and cognitive elements. It seems likely that this integration may largely occur at the level of the mPFC, involving interactions between IL and PL. As described, IL and PL strongly interconnect. In the rat, then, the IL/PL complex may exert significant control over emotional-cognitive aspects of behavior.

In summary, the mPFC of rats appears functionally homologous to a fairly widespread region of the prefrontal/frontal cortex of primates subserving motor, emotional, and cognitive elements of behavior; that is, the dorsal mPFC appears homologous to supplementary/premotor area, PL to dorsolateral PFC, and IL to the orbitomedial cortex of primates.

#### ACKNOWLEDGMENT

We thank Nediarka Todorova for superb technical assistance in all phases of this study.

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