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Combinatorial amygdalar inputs to hippocampal domains and hypothalamic behavior systems☆

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Abbreviations: AAA, anterior amygdalar area; ab, angular bundle; AB, accessory basal nucleus amygdala; ABs, accessory basal nucleus, superficial part; ac, anterior commissure; ACB, nucleus accumbens; AD, anterodorsal nucleus; ADP, anterodorsal preoptic nucleus; AHA, amygdalo-hippocampal area; AHNc,d,p, anterior hypothalamic nucleus, central, dorsal, posterior parts; AIp1-6, agranular insular area, posterior part, layers 1–6; alv, alveus; AM, anteromedial nucleus; amc, amygdalar capsule; AMY, amygdala; ANS, autonomic nervous system; AOB, accessory olfactory bulb; ARH, arcuate nucleus hypothalamus; AUDd,p,v, auditory areas, dorsal, primary, ventral areas; AV, anteroventral nucleus; AVPV, anteroventral periventricular nucleus; Bmg,pc, basal nucleus amygdala, magnocellular, parvicellular parts; BLAa,p, basolateral nucleus amygdala, anterior, posterior parts; BMAa,p, basomedial nucleus amygdala, anterior, posterior parts; BST, bed nuclei stria terminalis; CA1-3, fields of Ammon's horn; cc, corpus callosum; Cl,m, central nucleus amygdala, lateral, medial parts; CEAc,l,m, central nucleus amygdala, capsular, lateral, medial parts; CI, central intermediate nucleus; CL, central lateral nucleus; CLAv, claustrum, ventral region; CM, central medial nucleus; Coa, cortical nucleus amygdala, anterior part; Cop, cortical nucleus amygdala, posterior part; COAa,pl,pm1-3, cortical nucleus amygdala, anterior, posterolateral, posteromedial parts, layers 1–3; CP, caudoputamen; cpd, cerebral peduncle; CTX, cerebral cortex; CTXolf, olfactory cortex; DBB, nucleus of the diagonal band; DGlb,mb, dentate gyrus, lateral, medial blades; dhc, dorsal hippocampal commissure; DMHa,p, dorsomedial nucleus hypothalamus, anterior, posterior parts; ec, external capsule; ECT, ectorhinal area; En, endopiriform nucleus; ENTm,l, entorhinal area, medial, lateral parts; ENTmv, entorhinal area, medial part, ventral zone; EPd,v, endopiriform nucleus, dorsal, ventral parts; FC, fasciola cinerea; FF, fields of Forel; fr, fasciculus retroflexus; FS, striatal fundus; f-t, frontotemporal association system; fx, descending column fornix; GPe,i, globus pallidus, external, internal parts; hf, hippocampal fissure; HPF, hippocampal formation; HY, hypothalamus; I, intercalated nuclei amygdala; IA, intercalated nuclei amygdala; IAD, interanterodorsal nucleus; ihc, intrahippocampal circuit; int, internal capsule; L, lateral nucleus amygdala; LA, lateral nucleus amygdala; LH, lateral habenula; LHA, lateral hypothalamic area; lot, lateral olfactory tract; LPO, lateral preoptic area; LSd,i,v, lateral septal nucleus, dorsal, intermediate, ventral divisions; LSc,r,v, lateral septal nucleus, caudal, rostral, ventral divisions; LZ, lateral zone hypothalamus; Mc, medial nucleus amygdala, caudal subdivision; mam, mammillary region; MB, mammillary body; ME, median eminence; MEAad,av,pd, medial nucleus amygdala, anterodorsal, anteroventral, posterodorsal parts; MEPO, median preoptic nucleus; MH, medial habenula; MM, medial mammillary nucleus; MN, medial nuclei hypothalamus; mo, molecular layer; MOB, main olfactory bulb; MPF, medial prefrontal cortex; MPNl, medial preoptic nucleus, lateral part; MPO, medial preoptic area; MS, medial septal nucleus; mt, mtt, mammillothalamic tract; NLOT1-3, nucleus of the lateral olfactory tract, layers 1–3; och, optic chiasm; olf, olfactory; opt, optic tract; OT, olfactory tubercle; ot, optic tract; PA, posterior nucleus amygdala; PAA, piriform-amygdalar area; PACs, periamygdaloid cortex, sulcal region; PAR, parasubiculum; PC, piriform cortex; PERI, perirhinal area; PH, PHA, posterior hypothalamic nucleus; PIR1-3, piriform area, layers 1–3; PMd, dorsal premammillary nucleus; PMv, ventral premammillary nucleus; po, polymorph layer, dentate gyrus; POST, postsubiculum; PR, periventricular region hypothalamus; PRE, presubiculum; pro, preoptic region; PS, parastrial nucleus; PT, paratenial nucleus; PTLp, parietal region, posterior association areas; PVa,i,p, anterior, intermediate, posterior periventricular nucleus hypothalamus; PVHf,lp,mpd,pv, paraventricular nucleus hypothalamus, forniceal, lateral parvicellular, dorsal medial parvicellular, periventricular parts; PVHd, paraventricular nucleus hypothalamus, descending division; PVT, paraventricular nucleus thalamus; PX, caudoventral putamen; RCh, retrochiasmatic area; REcd,cm,cp, nucleus reuniens, caudal division, dorsal, median, posterior parts; Re, nucleus reuniens; rf, rhinal fissure; RSPd,v, retrosplenial area, dorsal, ventral parts; RT, reticular nucleus thalamus; S, subiculum; SBPV, subparaventricular zone; SC, superior colliculus; SCh, suprachiasmatic nucleus; SFO, subfornical organ; sg, granular layer, dentate gyrus; SH, septohippocampal nucleus; SI, substantia innominata; slm, stratum lacunosum-moleculare; slu, stratum lucidum; sm, stria medullaris; SNr, substantia nigra, reticular part; SOr, supraoptic nucleus, retrochiasmatic part; so, stratum oriens; sp, pyramidal layer; spd, deep pyramidal layer; sps, superficial pyramidal layer; SPFm, subparafascicular nucleus, magnocellular part; sr, stratum radiatum; SUBv, subiculum, ventral region; SUM, supramammillary nucleus; st, stria terminalis; StA, strial area; STN, subthalamic nucleus; STR, striatum; suo, supraoptic/anterior region; sup, supraoptic commissures; TEv, ventral temporal association areas; TMd, tuberomammillary nucleus, dorsal part; TR, postpiriform transition area; TS, triangular nucleus septum; TU, tuberal nucleus hypothalamus; TUte, tuberal nucleus, terete subnucleus; tub, tuberal region hypothalamus; V3r, third ventricle, periventricular recess; VA, ventral anterior nucleus; VAL, ventral anterior-lateral complex thalamus; VISal,all,am,lm,p,rl, visual areas, anterolateral, anterior laterolateral, anteromedial, mediolateral, primary, rostrolateral areas; VISC, visceral area cortex; VL, lateral ventricle; VM, ventral medial nucleus thalamus; VMHc,dm,vl, ventromedial nucleus hypothalamus, central, dorsomedial, ventrolateral parts; VPL, ventral posterolateral nucleus thalamus; VPM, ventral posteromedial nucleus thalamus; VTA, ventral tegmental area; ZI, zona incerta

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Abstract

The expression of innate reproductive, defensive, and ingestive behaviors appears to be controlled by three sets of medial hypothalamic nuclei, which are modulated by cognitive influences from the cerebral hemispheres, including especially the amygdala and hippocampal formation. PHAL analysis of the rat amygdala indicates that a majority of its cell groups project topographically (a) to hypothalamic behavior systems via direct inputs, and (b) to partly overlapping sets of hypothalamic behavior control systems through inputs to ventral hippocampal functional domains that in turn project to the medial hypothalamus directly, and by way of the lateral septal nucleus. Amygdalar cell groups are in a position to help bias or prioritize the temporal order of instinctive behavior expression controlled by the medial hypothalamus, and the memory of associated events that include an emotional or affective component.

Theme: Other systems of the CNS

Topic: Limbic system and hypothalamus

Keywords: Defensive behavior; Ingestive behavior; Reproductive behavior; Septal region; Subiculum

Contents

1. Introduction

The influential work of Klüver and Bucy [65] established an important role for the medial temporal lobes and adjacent regions of the cerebral hemispheres in modulating sexual, defensive, and ingestive behaviors — which are innate or hard-wired genetically, and are modified by life experiences encoded in the hemispheres. One part of the medial temporal lobe, the hippocampal formation (HPF), participates in the consolidation of episodic memory (e.g., [34,116,129,130,148]), whereas certain parts of the adjacent amygdala are specialized to modulate instinctive behaviors and the visceral/emotional responses coordinated with them (e.g., [11,21,30,36,47,61,76,79,81,128,155]). Recent high resolution structural analysis of medial hypothalamic circuits with PHAL, combined with earlier functional results, have begun to clarify the organization of distinct systems that appear to control the initiation of coordinated ingestive behaviors, as well as reproductive and defensive behaviors — that is, homeostatic and social behaviors [15,115,135]. This information has stimulated a detailed reexamination of how temporal lobe inputs to the hypothalamus are organized with respect to particular functional systems.

One outcome has been the characterization of topographic order in hippocampus to hypothalamus projections, especially those involved in 'relays' through the lateral septal complex [112,114,115]. Anterograde and retrograde axonal pathway tracing experiments indicate that distinct though partly overlapping domains along the dorsoventral (septotemporal, longitudinal) axis of the hippocampus proper/subiculum project in a topographically ordered way to components of the various hypothalamic behavior control systems, predicting that differential information processing or neural activity localized to particular HPF domains influences the temporal order displayed by particular classes of behavior. In other words, hippocampus to hypothalamus pathways are strategically placed to help prioritize the expression of alternative behavioral options over the course of time.

In this paper we present a detailed reexamination of topographic order in two other aspects of temporal lobe circuitry related either directly or indirectly to the hypothalamus. One involves the organization of direct projections from various cell groups of the amygdala to the hypothalamus, whereas the other involves the areal and laminar distribution of amygdalar projections to the HPF — which in turn projects to the hypothalamus. In an accompanying paper we consider how another aspect of this circuitry — projections from the amygdala to the bed nuclei of the stria terminalis — is organized [33]. Taken as a whole, this information provides a new model of amygdalar influences on hypothalamic systems. The functional dynamics of this circuitry remain to be characterized.

2. Amygdalar projections to the hypothalamus

Before describing the organization of axonal projections from the amygdala directly to the hypothalamus, it is useful to outline current models of hypothalamic and amygdalar structural subdivisions, along with what was learned about these projections with earlier generations of neuroanatomical pathway tracing methods.

2.1. Principles of hypothalamic and amygdalar organization

Models of hypothalamic and amygdalar functional organization continue to evolve rapidly as more and more is learned about their development, anatomical connections, neurotransmitter systems, and physiology. Our current working model of hypothalamic organization [115,135] is

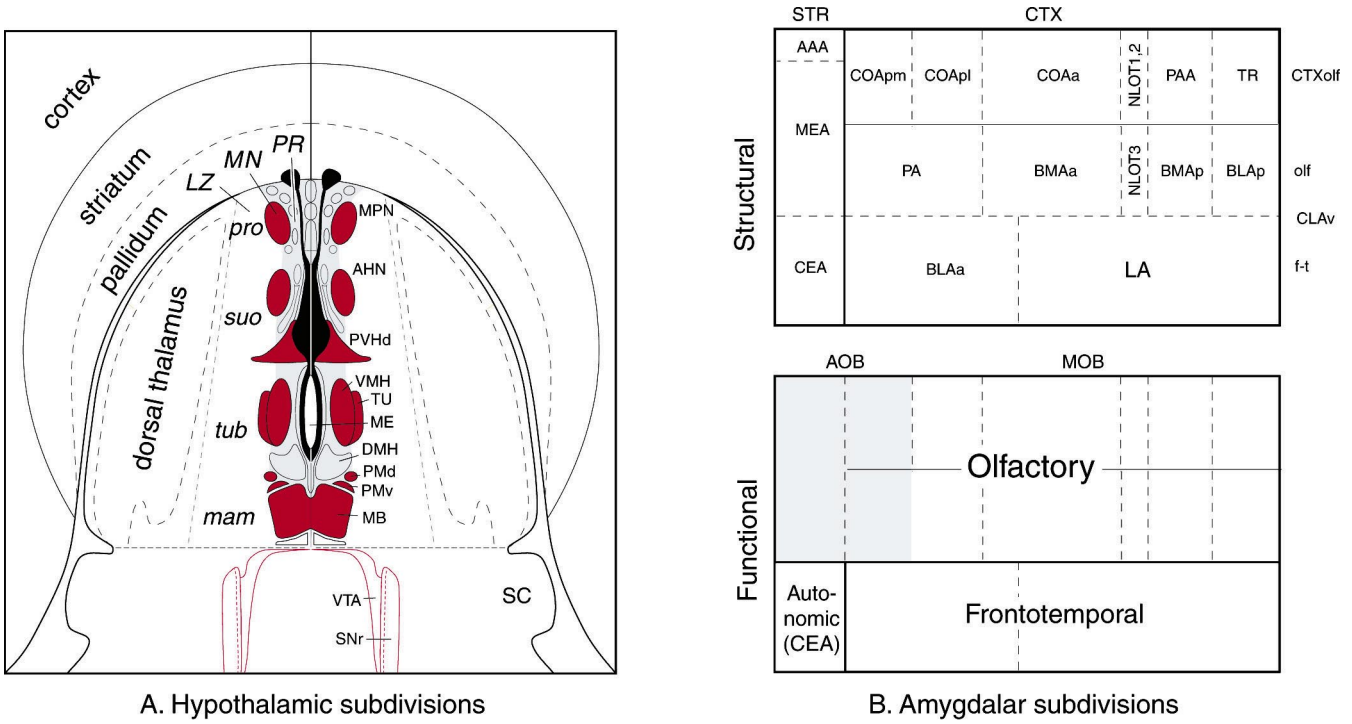
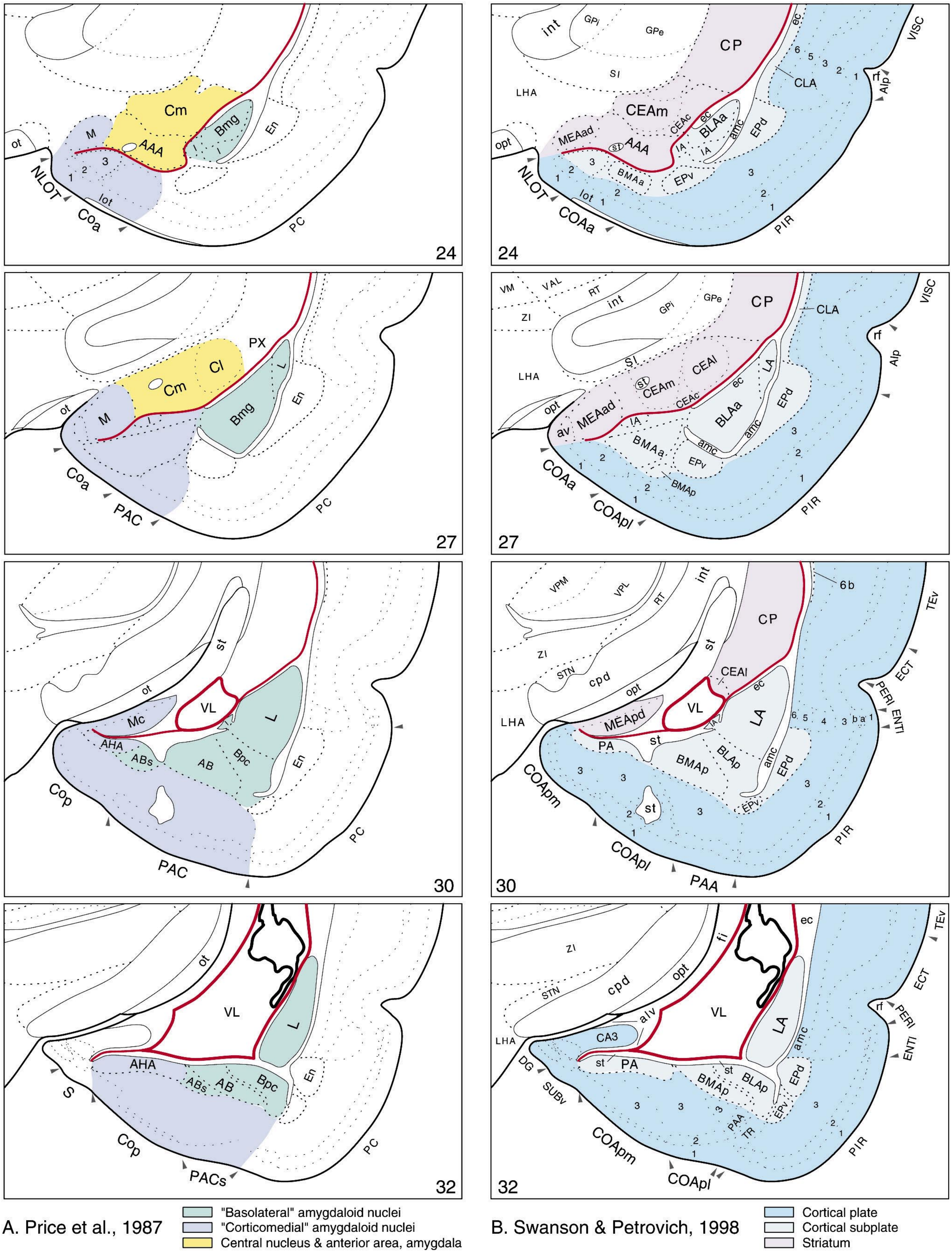


Fig. 1. Main subdivisions of the hypothalamus and amygdala. (A) The left side of this schematic flatmap shows the major longitudinal and transverse subdivisions of the hypothalamus. Four longitudinal zones are shown. The neuroendocrine motor zone is in black, on either side of the midline, surrounding the median eminence (ME) caudally. Between the motor zone and the column of medial nuclei (MN) lies a periventricular region (PR) that contains a highly differentiated visceromotor pattern generator network. The lateral zone (LZ) lies beyond the medial nuclei, adjacent to the thalamus. The larger medial nuclei serve as landmarks to divide somewhat arbitrarily the hypothalamus into four rostrocaudal regions or levels: preoptic (pro), supraoptic or anterior (suo), tuberal (tub), and mammillary or caudal (mam). Nuclei associated mainly with the medial hypothalamus are indicated on the right side. (B) Box diagrams to show the main structural and functional subdivisions of the amygdala. Structurally, the amygdala appears to consist of striatal and cortical divisions, with the latter further divided into cortical proper and cortical subplate (or claustral complex) components. Functionally, the various amygdalar cell groups appear to form parts of three major functional systems: olfactory (with main and accessory subsystems), autonomic, and frontotemporal cortical. Although unlabeled for simplicity, the cell groups in the functional diagram (bottom) are the same as those indicated in the structural diagram (top). Part (A) is adapted from Refs. [134,135] and Part (B) is adapted from Ref. [142].

best understood by starting with two longitudinal features: the neuroendocrine motor zone and the behavior control column (Fig. 1A). The former is centered in the classical periventricular zone and includes the well-known pools of neuroendocrine secretomotor neurons involved in the magnocellular (posterior pituitary) and parvicellular (anterior pituitary) systems, and the latter consists of a rostrocaudal series of distinct medial nuclei that control the expression of three classes of motivated behavior required for survival of the individual and the species. The descending division of the paraventricular nucleus (PVHd) is part of the mechanism controlling ingestive (eating and drinking) behavior, whereas reproductive behavior is controlled at least in part by three highly interconnected cell groups (medial preoptic, ventrolateral part of the ventromedial, and ventral premammillary nuclei), and defensive behavior is controlled at least in part by three other highly interconnected cell groups (anterior hypothalamic, dorsomedial part of the ventromedial, and dorsal premammillary nuclei).

The region of the hypothalamus between the neuroendocrine motor zone and medial nuclei contains a visceromotor pattern generator network with highly complex projections to nearby pools of neuroendocrine motoneurons and preautonomic cell groups. It occupies what we have recently called the *periventricular region*

Fig. 2. A graphical comparison of two widely used parcellations of the rat amygdala. The scheme in the left column views the amygdala as a structure within the cerebral hemisphere that has three divisions: the ‘basolateral’ nuclei, which are related connectionally with the neocortex; the ‘corticomedial’ nuclei, which are related to the olfactory system; and the central nucleus and anterior area, which are related to the autonomic system. The scheme in the right column regards the various amygdalar cell groups simply as parts of the cortical plate, cortical subplate, or striatum. An alternative to the left column for placing various amygdalar cell groups in cerebral functional systems is presented in Fig. 3. Note here that the two nomenclature schemes by and large agree on how to parcel the amygdala, while using different names. The most obvious differences are in the cortical region, where the scheme on the right has provided more subdivisions (see text for details). The comparison is made on the same series of transverse sections from our atlas of the rat brain [134], arranged from rostral (level 24) to caudal (level 32). The right column of the figure is adapted from Ref. [142], and the left column is based on the description in Ref. [111].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A. Price et al., 1987
"Basolateral" amygdaloid nuclei
"Corticomedial" amygdaloid nuclei
Central nucleus & anterior area, amygdala
B. Swanson & Petrovich, 1998
Cortical plate
Cortical subplate
Striatum

[135], which should be distinguished from the classical, generally much narrower *periventricular zone*. The largest cell group in the periventricular region is the dorsomedial nucleus, but many other smaller components (including the suprachiasmatic, anteroventral periventricular, and parastrial nuclei) are involved. Finally, the lateral zone of the hypothalamus remains poorly understood, but it almost certainly is involved in regulating behavioral state and levels of arousal.

Our current model of amygdalar organization [135,142] suggests that it is neither a structural nor a functional unit, but instead is an arbitrarily defined collection of adjacent cell groups in the cerebral hemispheres that was based originally on gross anatomy and Nissl stains. The model also suggests that it is more useful to place the various amygdalar cell groups within the context of major cerebral hemisphere divisions — either cerebral cortex or basal ganglia (cerebral nuclei, striatopallidum) — and then to define the organization of functionally defined systems involving these divisions (Fig. 1B). Thus, various parts of the amygdala appear, in the simplest scenario, to belong to one of three distinct telencephalic groups (Fig. 2B): caudal olfactory cortex (cortical amygdalar nuclei, piriform-amygdalar area, postpiriform transition area, and nucleus of the lateral olfactory tract), a thick ventromedial expansion of the claustral complex (lateral, basal, and posterior nuclei) that develops within the cortical subplate, and the caudoventral end of the striatum (central and medial nuclei, anterior amygdalar area, and intercalated nuclei). Viewed from the perspective of connections, these cell groups belong to the olfactory (main and accessory/pheromonal), autonomic, or 'frontotemporal' association cortical functional systems (Fig. 3). The name of the latter is somewhat misleading is so far as it actually includes a more or less continuous territory of association cortex starting rostrally in medial and orbital prefrontal regions and then extending caudally through agranular insular and ventral parietal regions, to ventral temporal association regions.

At present, two major schemes for naming the various cell groups associated with the amygdala are widely used, and a brief comparison of the two will make interpretation of the literature much easier for readers (Fig. 2). Our nomenclature has evolved from the classical descriptions of Johnston in 1923 [58], Brodal in 1947 [13], Cowan, Raisman, and Powell in 1965 [26], and Krettek and Price in 1978 [74]. Citations to the primary literature for each cell group we recognize are provided in Ref. [134]. There are only three substantive differences with the earlier treatment of Krettek and Price [74]. First, we further divide the 'periamygdaloid cortex' into posterolateral cortical nucleus (following Ref. [31]), piriform-amygdalar area (following Ref. [27]), and postpiriform transition area (following Ref. [45]). Second, we recognize a posterior amygdalar nucleus [16] instead of an amygdalo-hippocampal (transition) area. And third, we recognize an anterior part of the basomedial nucleus in the deep part of the anterior cortical nucleus, following De Olmos and colleagues [31].

The second major scheme in wide use today was elaborated by Price and colleagues in 1987 [111]. Their goal was to provide a unified parcellation scheme for rats, cats, and monkeys, and in doing so they referred to the basolateral nucleus as the basal nucleus, and the (posterior) basomedial nucleus as the accessory basal nucleus — adopting the primate nomenclature delineated in 1941 by Crosby and Humphrey [27], instead of applying their own earlier nomenclature [74] to the monkey. Unlike Price and colleagues [74], we do not recognize an accessory basal ('accessory basomedial') nucleus — in our scheme it seems to include the caudal tip of the anterior basomedial nucleus, lateral regions of the posterior nucleus, and medial regions of the posterior basomedial nucleus [16]. Thus far we have resisted applying primate terminology to the rat basolateral complex because of uncertainties about how valid assumptions concerning such homologies may be at this time (e.g., see Ref. [20], their p. 191).

Price and colleagues [111] divided amygdalar cell groups into three main divisions: the 'basolateral' nuclei (their lateral, basal, and accessory basal), which they suggested are heavily interconnected with neocortex; the 'corticomedial' nuclei (their periamygdaloid cortex, cortical and medial nuclei, and nucleus of the lateral olfactory tract), which are closely related to the main and accessory olfactory systems; and the central nucleus and anterior amygdaloid area, which they suggested are closely related to the autonomic system. Obviously, our current view of how amygdalar cell groups participate in cerebral functional circuitry is a variation on this theme, modified by more recent connectional information (Fig. 3). The only major difference is that we do not include the entire basolateral complex in the system related primarily to the neocortex or isocortex. Instead, we restrict this to the lateral and anterior basolateral (magnocellular basal) nuclei; the rest we suggest are more closely related to the main and accessory olfactory systems.

One seemingly minor refinement of our recent model of amygdalar organization [142] has become apparent, and should be mentioned here. The connections of the dorsal region of the traditional [86] capsular part of the central amygdalar nucleus (CEAc) differ dramatically from those associated with the rest of the CEA. First, the dorsal CEAc shares massive bidirectional connections with the same regions of frontal and temporal cerebral cortex that are bidirectionally connected with the lateral and anterior basolateral nuclei of the amygdala (our frontotemporal group; Fig. 1B) [85,90,117]. Second, the dorsal CEAc apparently does not project to other parts of the CEA (results of PHAL experiment illustrated in Ref. [33], their Figs. 4 and 5), unlike, for example, the CEAl [107]. And third, the descending output of the dorsal CEAc is very similar to that of the dorsal striatum — it projects to

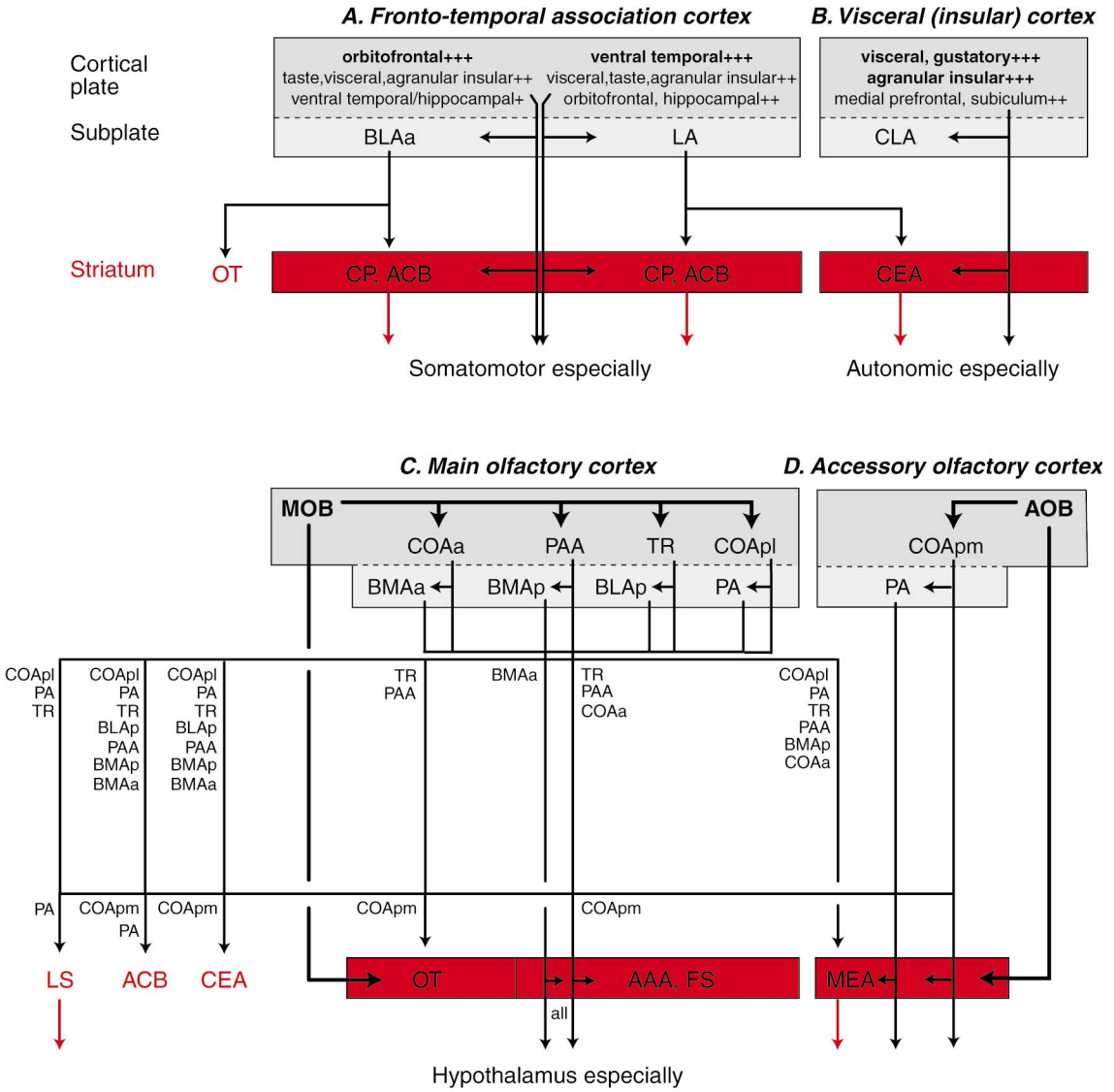


Fig. 3. Amygdalar cell groups are associated with four distinct corticostriatal systems. (A) One system involves the lateral and anterior basolateral nuclei (of the subplate or claustral division of cortex), which receive their major cortical plate inputs from orbitofrontal and temporal association areas, and project massively to the caudoputamen, nucleus accumbens, and central amygdalar nucleus parts of the striatum. To keep (A) simple, association connections within the cortical plate and subplate, and the full range of cortical plate inputs to the striatum, are not shown. (B) A second system involves cortical inputs to the central amygdalar nucleus, which preferentially innervates autonomic-related parts of the brainstem. The most dense cortical inputs arise in the visceral and gustatory areas, and in the agranular insular area, which is a visceral association area. (C and D) The other two systems include major parts of the main (C) and accessory (D) olfactory systems, which are conveniently defined in terms of massive inputs from the main and accessory parts of the olfactory bulb, respectively. Note that the fronto-temporal association cortex-striatal system tends to innervate somatomotor elements of the brainstem-cord, whereas the visceral cortical-striatal system tends to innervate autonomic-related elements in the brainstem, and the olfactory systems tend to innervate the hypothalamus. Complete documentation for the pathways shown here is found in Refs. [87,135,142].

restricted regions of the medial segment of the globus pallidus and to the substantia nigra (G.D. Petrovich, L.W. Swanson, unpublished observations; see PHAL injection site in Figs. 4 and 5 of Ref. [33]). Based on this evidence, it seems most parsimonious to remove the ‘dorsal CEAc’ from the CEA altogether. It should be noted that Price and colleagues [111] had assigned this dorsal region of the capsular central nucleus to the caudoventral putamen.

2.2. The earlier literature

Although amygdalar projections through the stria terminalis to the hypothalamus were first observed by early workers in normal material, their precise distribution was hardly possible to ascertain [62]. Later use of the experimental Nauta method provided somewhat equivocal results in primates, although projections to the medial

preoptic and anterior hypothalamic areas were clearly demonstrated in rats [26]. Then application of the Fink–Heimer modification of Nauta's method showed that fibers in the stria terminalis generate dense terminal fields in the anterior hypothalamic, ventromedial, and ventral premammillary nuclei of rats [32,46,99]. In addition, degeneration methods revealed a sparse projection through the ventral amygdalofugal system (a component of the ansa peduncularis [10]) to the rostral half of the hypothalamic lateral zone [99]. However, a new era was ushered in with the landmark autoradiographic analysis of Krettek and Price [73], who showed how individual amygdalar cell groups in rat and cat project to the hypothalamus. Their results indicated that the medial, basomedial, and posterior amygdalar nuclei (of our terminology) project to the ventromedial nucleus; that these same nuclei along with the posterior cortical nucleus project to the premammillary nuclei; and that the central and basolateral nuclei project sparsely to the rostral lateral hypothalamic zone.

However, most of our detailed knowledge is based on experiments using contemporary pathway tracing techniques (especially the PHAL method) that are relatively very sensitive, allow for clear distinctions between terminal fields and fibers-of-passage, and provide high resolution in terms of small, clearly-defined injection sites (cells of origin) and their corresponding terminal fields [134]. A number of amygdalohypothalamic projections from our collection of about 125 PHAL experiments in the rat have been described recently [16,19,106,107,142]. The results of this work will be reviewed briefly and hypothalamic inputs from three other amygdalar cell groups (posterior basolateral nucleus, medial central nucleus, and anterior amygdalar area) will be described in some detail. The articles just cited contain extensive reviews of the earlier neuroanatomical literature that seems relevant, as well as documentation of the PHAL method as we have used it.

Overall, amygdalar cell groups send massive, topographically organized projections to the medial nuclei and less extensive inputs to the neuroendocrine motor zone, region of the visceromotor pattern generator network, and caudal half of the lateral zone. We have found that it is much easier to understand the organization of these projections if they are described in terms of the functional systems with which the various amygdalar cell groups are most closely associated.

2.3. Projections from the frontotemporal system

For simplicity, we begin with these two parts of the amygdala (lateral and anterior basolateral nuclei) because there is no evidence — from the literature [73] or from our published and unpublished observations on brains with PHAL injections in both cell groups — that they project significantly to the hypothalamus (Fig. 4), or even to the bed nuclei of the stria terminalis, which in turn project to the hypothalamus [138].

In contrast, we shall see below (Section 3.2) that the lateral nucleus provides one of the heaviest amygdalar inputs to the HPF, including direct projections to domains in the ventral subiculum and field CA1 that in turn influence the hypothalamus directly, and via projections to the lateral septal nucleus. The anterior basolateral nucleus is unique in that it only sends a few axons to the HPF, instead massively innervating the dorsolateral caudoputamen and premotor cortical areas, which are avoided by the rest of the amygdala [64,104]. Thus, the anterior basolateral nucleus, unlike the rest of the amygdala, projects neither to the hypothalamus nor to the hippocampus but instead provides a unique output to obvious components of the somatomotor corticostriatal system.

Interestingly, ventrolateral regions of the lateral nucleus receive dense inputs from the dorsomedial and ventrolateral parts of the hypothalamic ventromedial nucleus [18], which are part of hypothalamic controllers for defensive and reproductive behaviors, respectively (Section 2.1). As we shall see below, these parts of the ventromedial nucleus receive heavy inputs from the main olfactory system via the amygdala and/or HPF (Sections 2.5 and 3.4) but hardly project back to them [18]. On the other hand, the main amygdalar parts of the frontotemporal association system do project substantially to the main and accessory olfactory systems. The lateral nucleus innervates most amygdalar parts of the main and accessory olfactory systems, although heaviest terminal fields are generated in the posterior basomedial nucleus and piriform-amygdalar area (see Ref. [109], and our unpublished observations); whereas the anterior basolateral nucleus projects most substantially to the posterior basolateral nucleus [104,124]. Thus, projections from the hypothalamic ventromedial nucleus to the amygdala appear to converge with frontotemporal cortical information before transmission to the olfactory system.

2.4. Projections from the autonomic system

The structural and functional roles of the central amygdalar nucleus in the brain system that controls the output of the autonomic nervous system are widely known [80,142]. This is certainly not to say, however, that the central nucleus cannot influence other systems as well. For example, it plays a role in modulating somatomotor responses in a conditioned startle paradigm [29,66,120], and it can influence dorsal striatal function [44] via direct inputs to the compact part of the substantia nigra [38,49,73,152,159].

It has been reported for over two decades that the central nucleus innervates preferentially the lateral rather than the medial hypothalamus in rat, cat, and monkey [73,110]. Nevertheless, the exact distribution of this projection, and

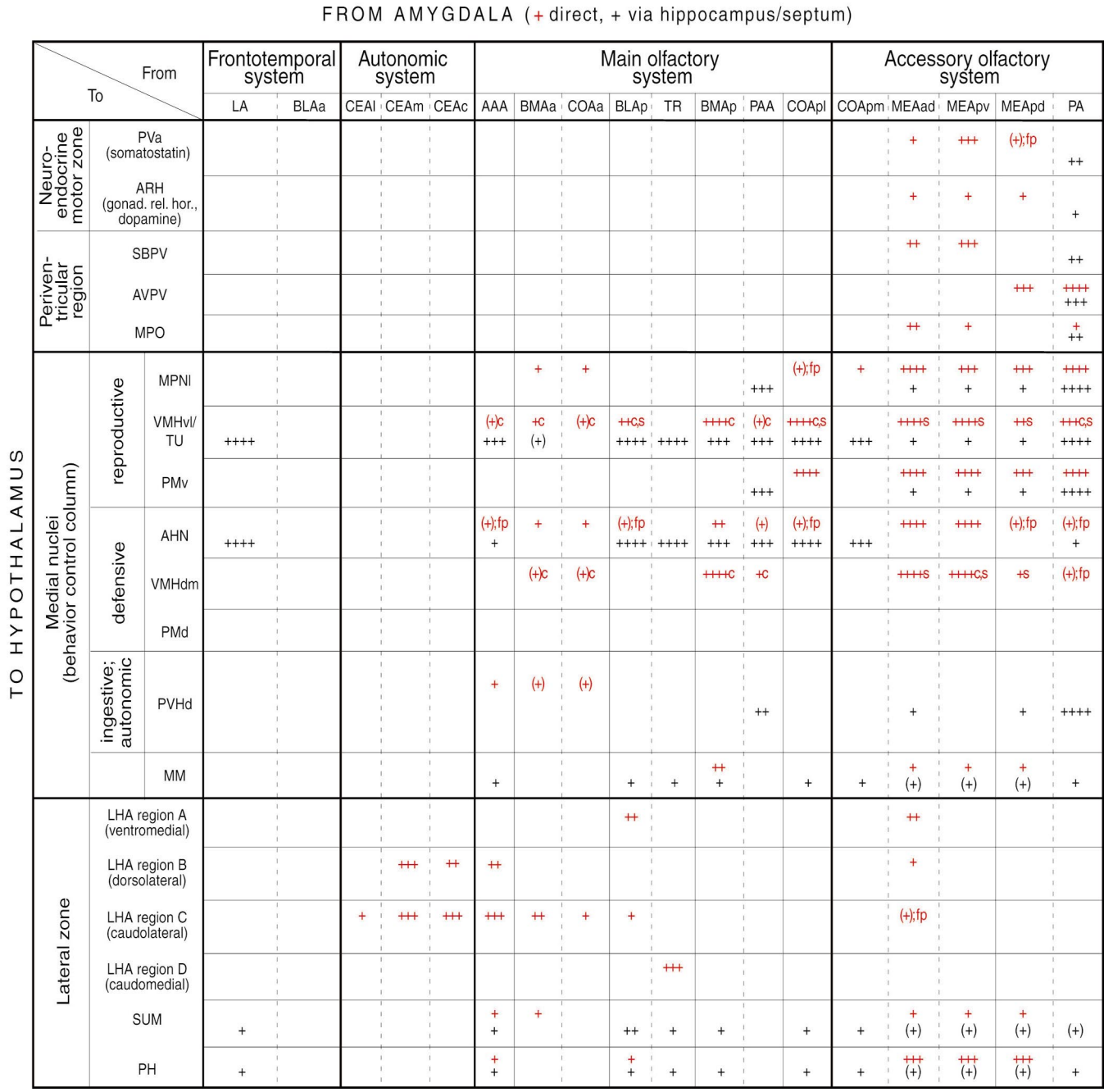
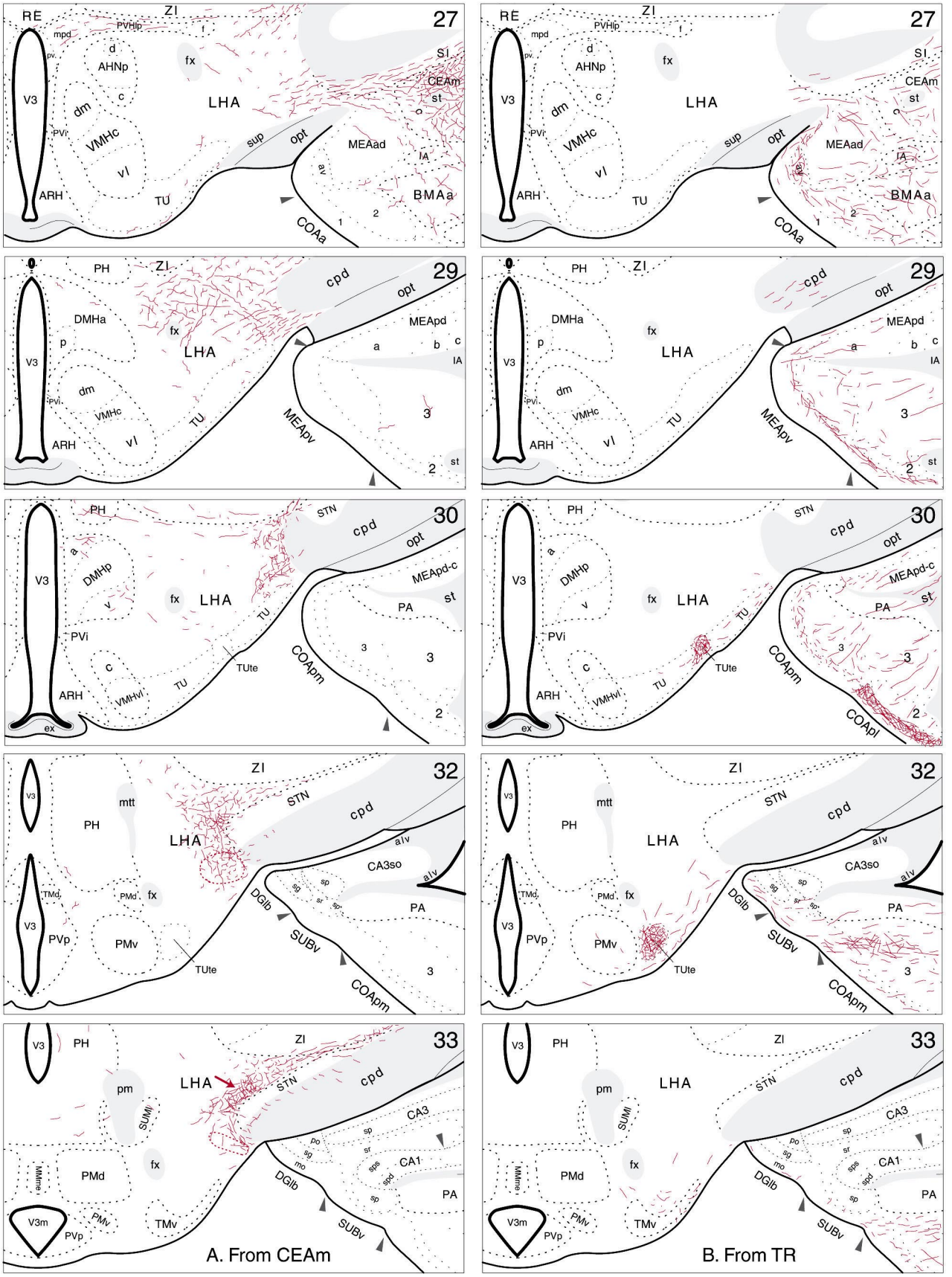


Fig. 4. Organization of anatomically defined projections from the amygdala (columns) to the hypothalamus (rows) in adult male rat. Direct projections from amygdala to hypothalamus are shown as red crosses, whereas indirect projections from the amygdala to the hippocamposeptal system and then to the hypothalamus are shown as black crosses. The crosses indicate relative strength of connections in qualitative terms: ++++, very dense; +++, dense; ++, moderate; +, light; (+), sparse. Blank boxes indicate no PHAL labeling was observed. The locations of hypothalamic lateral zone areas A–D are indicated in Fig. 5. Abbreviations: *c* and *s* refer to the cellular core and shell of the ventromedial nucleus, respectively; *fp* indicates apparent fibers-of-passage.

possible topographical organization of terminal fields from various parts of the central nucleus have remained vague until recent PHAL analyses. For example, the only distinct hypothalamic terminal field arising in the very circumscribed lateral part of the central nucleus [107] consists of a few terminal boutons in the ventrolateral lateral hypothalamic area centered in the parasubthalamic nucleus of Wang and Zhang [153] (Fig. 4). However, the most dense central nuclear projections to the lateral hypothalamus arise in the medial and capsular parts.

Projections from the medial part of the central nucleus to the hypothalamus are illustrated in Fig. 5A, where it is obvious that there are two major terminal fields. One is in the dorsolateral region (at the level of the dorsomedial and


RE
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27
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BMAa
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PH
29
cpd
DMHa
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MEApd
a
b
c
MEApv
3
30
STN
MEApd-c
PA
TUte
COApm
COApl
ex
32
mtt
CA3so
PMd
PMv
PVp
DGlb
SUBv
sp
sg
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slv
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A. From CEAm
B. From TR

Fig. 5.

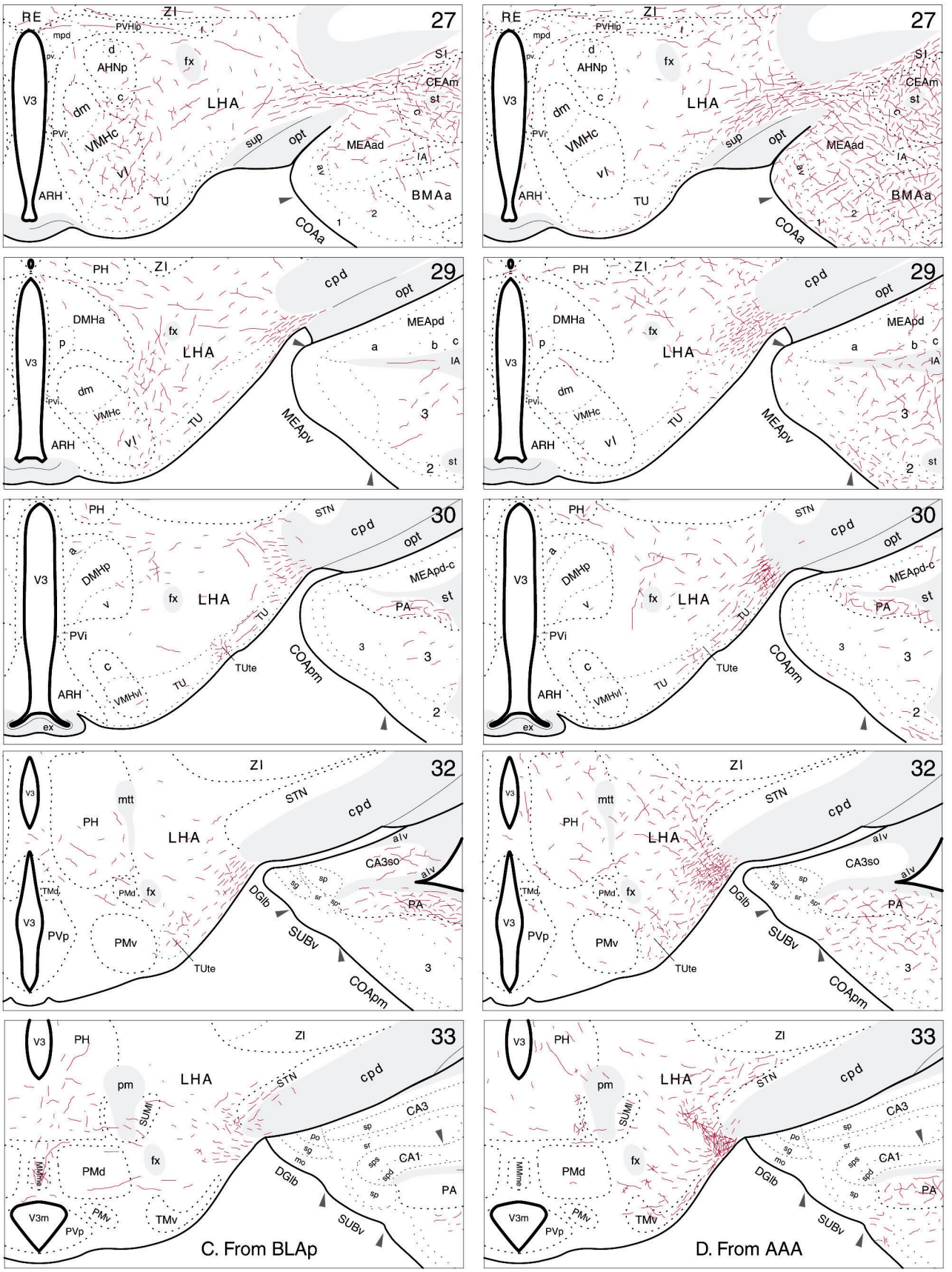


Fig. 5. (*continued*)

posterior nuclei, level 29) that we shall see also receives inputs from the main (posterior basolateral nucleus) and accessory (anterodorsal medial nucleus) olfactory components of the amygdala (Fig. 4, LHA region B). The other, even more dense and circumscribed terminal field, is in caudolateral regions of the lateral hypothalamic area centered in the parasubthalamic nucleus (especially dorsolaterally, arrow in Fig. 5A, level 33), which also receives inputs from the main olfactory system (Fig. 4, LHA region C). However, note in Fig. 5A, levels 30–33, that this terminal field is not confined to the parasubthalamic nucleus — for example, it is quite dense just rostral to the parasubthalamic nucleus, at level 30. A very light input to the hypothalamic paraventricular nucleus was reported earlier [40].

PHAL injections centered in, and essentially restricted to, ventral (experiment 94) and lateral (experiment 84) regions of the capsular central nucleus (Figs. 4 and 5 in Ref. [33]) also project selectively to the dorsolateral and caudolateral terminal fields (Fig. 4) in a way that is qualitatively similar to that illustrated for the medial central nucleus (as illustrated in Fig. 5A). However, there are some subtle differences. First, lateral regions of the capsular central nucleus innervate dorsolateral regions of the parasubthalamic nucleus itself (indicated by the arrow in Fig. 5A, level 33), but in addition there is an obvious plexus of terminals just ventral to the latter (indicated by a dashed outline in Fig. 5A, levels 32 and 33). Second, ventral regions of the capsular central nucleus also innervate the caudolateral region as shown for the medial central nucleus, except for the obvious plexus in the dorsolateral parasubthalamic nucleus (arrow in Fig. 5A, level 33). And third, an input to the dorsolateral terminal field (Fig. 4, lateral region B; Fig. 5A, level 29) appears to be lighter from the lateral capsular central nucleus than from the ventral capsular and medial central nucleus.

It is worth pointing out that the region of the lateral hypothalamic area innervated by the central nucleus corresponds rather precisely to the region containing labeled neurons after retrograde tracer injections in the dorsal vagal complex and spinal cord [141], the region of the lateral hypothalamus that innervates autonomic cell groups in the brainstem and spinal cord [121]. While many neurons in this region of the lateral hypothalamus do not project to the dorsal vagal complex and spinal cord [141], these results support evidence that it plays an important role in initiating autonomic responses that accompany conditioned fear [78].

2.5. Projections from the main olfactory system

Whereas the lateral and anterior basolateral amygdalar nuclei (related to the frontotemporal association system) have no direct inputs to the hypothalamus, and the central nucleus (related to the autonomic system) projects to the hypothalamic lateral zone, main olfactory components of the amygdala project to both the hypothalamic lateral zone and the medial nuclei of the behavior control column (Fig. 4). Five distinct cortical areas that receive a massive input from the main olfactory bulb (the anterior and posterolateral cortical nuclei, nucleus of the lateral olfactory tract, postpiriform transition area, and piriform-amygdalar area), along with associated parts of the claustral complex, and a poorly defined region of the striatum (anterior amygdalar area), are found within the amygdala (Fig. 1B).

Hypothalamic projections from the anterior cortical nucleus and associated anterior basomedial nucleus are very similar [106]. They lightly innervate most components of the ingestive, reproductive, and defensive behavior control column, and also send an input to a circumscribed region of the caudolateral lateral hypothalamic area (region C in Fig. 4). The projection to this region from the anterior basomedial nucleus resembles that from the anterior amygdalar area (see Fig. 5D, levels 30–33), except that it is more uniform; that is, it is not particularly dense ventrally. The input to this region from the anterior cortical nucleus is lighter, and is concentrated just dorsal and ventral to the parasubthalamic nucleus itself, which contains very few labeled axons. The parasubthalamic nucleus generates massive inputs to most parts of the central autonomic system [39], and the anterior cortical and anterior basomedial nuclei are also closely related to the autonomic system via inputs to the central amygdalar nucleus, bed nuclei of the stria terminalis, and tuberal levels of the lateral hypothalamic area [105].

A second component of the main olfactory system, the

Fig. 5. Projections from amygdalar cell groups to the caudal hypothalamus, labeled with PHAL (red). The results are plotted on standard atlas drawings of the rat brain [134], arranged from rostral to caudal (A is atlas level 27, B level 29, and C level 32). (A) Projections from the medial part of the central amygdalar nucleus. The injection site of this experiment is illustrated in Figs. 4 and 5 of Ref. [33]. The dashed outline in levels 32 and 33 indicates the location of an additional terminal plexus labeled from lateral regions of the capsular central nucleus (experiment 84). The arrow in level 33 indicates a plexus that was not so obviously labeled from ventral regions of the capsular central nucleus (experiment 94). (B) Projections from the postpiriform transition area as observed in experiment 59, although the same pattern was seen in three other experiments with a PHAL injection centered in various regions of this area. The terminal field ends just caudal to the level indicated (it is not present at atlas level 33), and extends rostrally to atlas level 30 in exactly the same position relative to the fornix and base of the brain, except that it becomes progressively smaller in cross-sectional area. As compared to the definitive, medial part of the ventral premammillary nucleus, the area containing this terminal field has more myelinated fibers as observed under darkfield illumination, and the neurons have less tendency to display a vertical orientation (although they are about the same size, and have about the same packing density, as those in the definitive ventral premammillary nucleus). The lateral border of this cell group (labeled here the terete subnucleus of the tuberal nucleus, TUte) is formed by a very obvious fiber tract lying on the base of the brain. (C) Projections from the posterior basolateral nucleus of the amygdala; the injection site of this experiment is illustrated in Fig. 17 of Ref. [33]. (D) Projections from the anterior amygdalar area; the injection site of this experiment is also illustrated in Fig. 17 of Ref. [33].

postpiriform transition cortical area and associated posterior basolateral nucleus, appear to have even more restricted projections to the hypothalamus. In fact, the only projection from the postpiriform transition area identified thus far to the hypothalamus ends in a distinct ventral caudomedial region that could be regarded either as a lateral division of the ventral premammillary nucleus (level 32 in Ref. [134]) or as an intermediate division of the tuberal nucleus (level 30 in Ref. [134]). The region containing this terminal field seemingly corresponds to at least the rostral three-quarters or so of the terete nucleus identified by Paxinos and Watson [103], and its small neurons are readily observed in Nissl-stained material, especially when viewed with darkfield illumination. Thus, it has been labeled the terete subnucleus of the tuberal nucleus in Fig. 5 (see TUte in levels 30 and 32 of Fig. 5B). In contrast, the posterior basolateral nucleus sends clear projections to the ventrolateral part of the ventromedial nucleus (reproductive behavior) and to a circumscribed ventromedial region in tuberal levels of the lateral hypothalamic area, between the ventromedial nucleus and the level of the fornix (region A in Fig. 4, level 29 in Fig. 5C) — which, as we shall see, also receives a distinct input from the anterodorsal part of the medial amygdalar nucleus. The posterior basolateral nucleus also sends a few terminals to the caudolateral lateral hypothalamic area (region of the parasubthalamic nucleus), terete subnucleus, and posterior hypothalamic nucleus.

The piriform-amygdalar cortical area and closely associated posterior basomedial nucleus form a third amygdalar component of the main olfactory system. The piriform-amygdalar area sends a few axons to the reproductive and defensive behavior control nuclei in the medial hypothalamus (see PHAL injection site in Fig. 17 of Ref. [33], and Fig. 4 here), whereas the behavior control column is heavily innervated by the posterior basomedial nucleus. Specifically, the latter sends moderate to very dense projections to the cellular core of both major parts of the ventromedial nucleus, to the tuberal nucleus, to the anterior hypothalamic nucleus, and to the medial mammillary nucleus [105].

The posterolateral cortical nucleus and part of the posterior nucleus constitute a fourth olfactory cortex/'claustral complex' pair in the amygdala. The posterolateral cortical nucleus is somewhat unusual in that whereas it receives a massive input to the outer molecular layer from the main olfactory bulb [125], it is also massively interconnected with the three amygdalar components of the accessory olfactory system: the posteromedial cortical, medial, and posterior nuclei [16,19]. As indicated in Fig. 4, the vast majority of hypothalamic projections from the posterolateral cortical nucleus are directed to massive terminal fields in the ventrolateral ventromedial nucleus (both the cellular core and the shell), tuberal nucleus, and ventral premammillary nucleus — major components of the reproductive behavior control column. Similar projections from the posterior amygdalar nucleus will be discussed in the next section.

The fifth amygdalar component of main olfactory cortex/claustrum is represented by the nucleus of the lateral olfactory tract. Our PHAL collection does not include injections of this cell group, and there appears to be little if any suggestion in the literature that it projects to the hypothalamus.

Finally, we come to the still rather obscure anterior amygdalar area, which receives inputs from components of the main olfactory system — the piriform area [82], anterior cortical nucleus [105], and anterior basomedial nucleus [105] — and the accessory olfactory system, especially all parts of the medial amygdalar nucleus [19]. As shown in Figs. 4 and 5D, the main hypothalamic projection targets of the anterior amygdalar area are centered in the caudal half of the lateral zone. One terminal field lies caudolaterally, centered just ventral, and to some extent lateral, to the parasubthalamic nucleus (Fig. 5D, levels 30–33), whereas the other is centered dorsolaterally, in a rather extensive region at the level of the dorsomedial and posterior hypothalamic nuclei, dorsal to the fornix column.

2.6. Projections from the pheromonal system

Parts of the amygdala associated with the pheromonal system innervate all major functional zones of the hypothalamus (Fig. 4). The posteromedial cortical nucleus and medial nucleus are the major cortical and striatal targets of the accessory olfactory bulb, respectively [125,142], and we have suggested that the posterior amygdalar nucleus (amygdalo-hippocampal area) is a part of the claustral complex/subplate associated with the posterior cortical nucleus (see Fig. 1B). The posteromedial cortical nucleus, which sends a massive, presumably glutamatergic projection to all parts of the medial nucleus, also innervates lightly the medial preoptic nucleus of the reproductive behavior control circuit (Fig. 4) [16].

Although there are at least four parts of the medial nucleus, only three of them (posterodorsal, posteroventral, and anterodorsal) are large enough to have been examined thoroughly with the PHAL method [19]. The posterodorsal part densely innervates all components of the medial hypothalamic reproductive behavior control network, and only very lightly innervates the anterior hypothalamic nucleus component of the defensive behavior control network (Fig. 4). In contrast, the posteroventral and anterodorsal parts generate the most extensive hypothalamic innervation of any amygdalar cell group. They densely innervate all components of both the reproductive and defensive behavior control networks (except, noticeably, the dorsal premammillary nucleus), and send inputs to various regions of the hypothalamic lateral zone, including especially the posterior hypothalamic nucleus (Fig. 4).

In addition, all three parts of the medial amygdalar

nucleus innervate the region of the neuroendocrine motor zone and the periventricular region that contains a visceromotor pattern generator network (Fig. 4). The posteroventral part sends an especially dense input to the anterior periventricular nucleus, which contains abundant neuroendocrine somatostatin neurons, whereas all three parts send a light input to the arcuate nucleus, which contains neuroendocrine dopamine and growth hormone-releasing hormone neurons [84]. Whether neuroendocrine motoneurons are innervated directly by inputs from the medial amygdalar nucleus remains to be determined ultrastructurally. With respect to the periventricular region, it is important to note that the posterodorsal part densely innervates the anteroventral periventricular nucleus, which appears to play a critical role in generating the reproductive cycle via the gonadotropin surge [41], and that the anterodorsal and posteroventral parts innervate the subparaventricular zone, which receives a massive input from the suprachiasmatic nucleus and is thought to play an important role in imposing circadian rhythms on its projection targets [154].

The posterior amygdalar nucleus also generates a substantial projection to the hypothalamus that is obviously related to reproductive function (Fig. 4) [16]. Thus, like the posterodorsal part of the medial amygdalar nucleus, it heavily innervates the anteroventral periventricular nucleus, along with all three major parts of the reproductive component of the behavior control column. As far as the ventrolateral ventromedial nucleus is concerned, the posterior nucleus innervates both the cellular core and the shell, unlike the medial amygdalar nucleus, whose various parts send most of their input to the shell (except for the posteroventral part, which also innervates substantially the core of the ventrolateral part of the ventromedial nucleus).

One part of the hypothalamus, the ventral premammillary nucleus, projects heavily to amygdalar parts of the accessory olfactory system, specifically to the posterodorsal medial nucleus and the posterior nucleus [17].

2.7. Conclusions

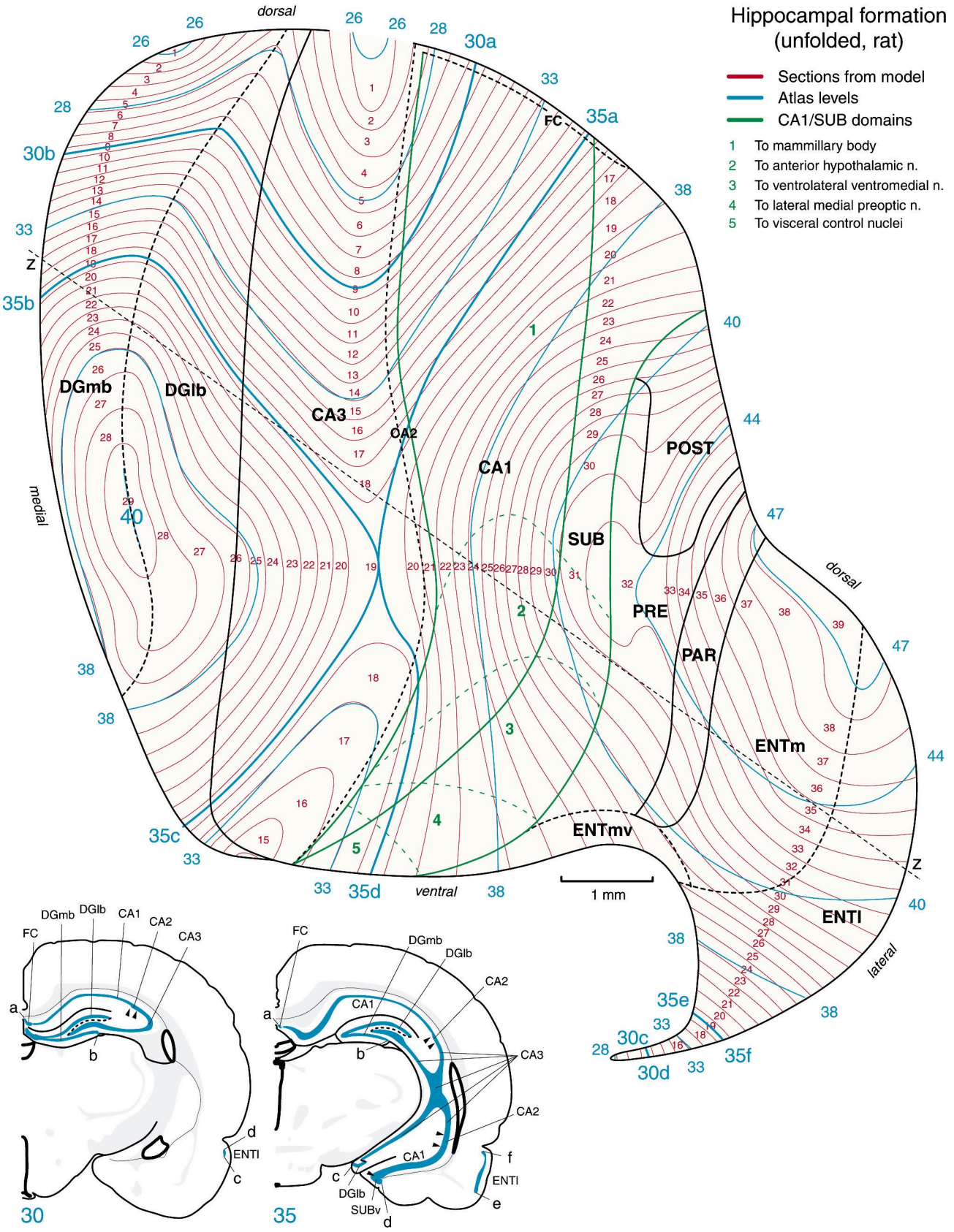
First and foremost, the connectional data indicate that amygdalar components of different functional systems project to different functional systems within the hypothalamus. Overall, amygdalar cell groups that are part of the frontotemporal association cortical system do not project directly to the hypothalamus (or even the bed nuclei of the stria terminalis), those that are part of the autonomic system (various parts of the central nucleus) innervate substantially only the lateral zone, those that are part of the main olfactory system innervate the behavior control column and lateral zone, and those that are part of the pheromonal system innervate the neuroendocrine motor zone, visceromotor pattern generator, behavior control column, and lateral zone.

3. Amygdalar projections to the hippocampal formation

The amygdala and HPF lie adjacent to one another in the region of the medial temporal lobe, and historically they have been linked to a variety of similar functions including olfaction, emotion, and episodic memory (e.g., [65,83,95,98,133,155]). Until relatively recently their conjoint action was thought to be required for certain types of learning (e.g., [6,93,122]), although this view has now been challenged with rather compelling evidence that the two regions are involved in differentiable aspects of learning and/or memory (e.g., [7,29,75,91,160]).

Nevertheless, there are connections traveling in both directions between the amygdala and HPF. For example, electrophysiological evidence demonstrates that information processed within the amygdala reaches the HPF [24,35], where it appears to modulate synaptic activity [53,54,147] and thus function [101,119]. Anatomical evidence for amygdalar projections to the HPF was reported by Gurdjian almost 75 years ago in the rat [42], although initial analysis of topographic organization within this pathway or set of pathways awaited autoradiographic analysis by Krettek and Price in 1977 [72]. Their results indicated that, in the rat and cat, the lateral nucleus and periamygdaloid region (PAC in Fig. 2) project to ventral regions of the lateral entorhinal area (specifically to layers 3 and 2, respectively), the posterior basolateral nucleus and periamygdaloid region project to the ventral subiculum, and the posterior basolateral nucleus also innervates a restricted posterodorsal zone of the parasubiculum. These results were of particular interest insofar as superficial layers of the lateral entorhinal area generate the lateral perforant path and alvear path to the hippocampus proper and dentate gyrus [48,131], the ventral subiculum generates the medial corticohypothalamic tract to the hypothalamus [136,137], and the parasubiculum contributes to

Fig. 6. Flatmap of the adult rat hippocampal formation. Note that the topology of this vast region is a series of adjacent cortical strips arranged from medial (dentate gyrus) to lateral (entorhinal area). Thus, each cortical area has a longitudinal (dorsoventral or septotemporal) and transverse (mediolateral or proximodistal) axis, with the basic intrahippocampal (trisynaptic) circuit arranged along the transverse axis (see Fig. 18 and Ref. [140]). The disposition of hippocampal cell layers in histological sections (numbered 1–28) that were used to make the physical model are shown in red, the disposition of hippocampal cell layers in levels (numbered 26–47) from our atlas [134] are shown in blue, and hypothetical functional domains in field CA1/subiculum [112] are shown in green. Two atlas levels (30 and 35) are shown in the lower left, with the major hippocampal cell layers used to construct the physical model highlighted in blue; note how they are disposed on the unfolded map. This basic approach to HPF organization goes back to the work of Blackstad in the 1950s [9]. The approximate location of the hypothetical unfolded HPF lamination map (Fig. 8) is indicated by dashed line z,z.


Hippocampal formation
(unfolded, rat)
Sections from model
Atlas levels
CA1/SUB domains
1 To mammillary body
2 To anterior hypothalamic n.
3 To ventrolateral ventromedial n.
4 To lateral medial preoptic n.
5 To visceral control nuclei
dorsal
ventral
medial
lateral
DGmb
DGlb
CA3
CA2
CA1
SUB
POST
PRE
PAR
ENTm
ENTmv
ENTl
FC
1 mm
30
35

the postcommissural fornix projection to the mammillary bodies [136,137].

Somewhat later anatomical studies in the cat [118] and monkey [1,4,123] suggested that the basomedial nucleus may also project to the HPF, and that amygdalar projections may extend well into ammonic field CA1. However, most of this evidence was based on the autoradiographic technique, which has a major disadvantage in laminated structures such as the HPF where fibers-of-passage are often indistinguishable from terminals, so that the actual site of amygdalohippocampal terminal fields was often unclear. Thus, we undertook a reexamination of this problem in our collection of experiments involving PHAL injections targeting all of the various amygdalar cell groups except the nucleus of the lateral olfactory tract and intercalated nuclei (Section 2.1). Preliminary results have been reported elsewhere [104,105], and material presented here will be compared with a similar analysis of basolateral complex projections published in the meantime [108].

We shall see that at least 11 cell groups associated with the amygdala project to the HPF. The topography of these amygdalohippocampal pathways will then be explored to indicate qualitatively how they may influence particular regions of the hypothalamus via (a) the intermediary of topographically organized hippocamposeptal projections [112,114,137], and (b) direct hippocampo-hypothalamic projections [20,63,70,136,137]. One goal of this analysis is to compare the distribution of direct and indirect projections to various functional systems of the hypothalamus from individual amygdalar cell groups (Fig. 4).

3.1. Principles of hippocampal organization

It is notoriously difficult to appreciate topographic features of fiber and terminal distributions within the HPF because of the unusual extent of folding that it undergoes during development [3]. Therefore, we have presented the results of our PHAL experiments in three different ways (aside from photomicrographs). First, projections have been plotted on a standard series of atlas templates through the HPF, which renders detailed comparisons of terminal field extent and laminar distribution considerably easier between experiments [134]. Second, the results have been plotted onto an unfolded map of the HPF, which makes qualitative comparisons between overall distribution patterns within the HPF easier [144]. And third, the laminar distribution of the various amygdalohippocampal projections has been summarized on an idealized slice through the unfolded HPF [140].

The unfolded map of the HPF was derived from a large physical model of the rat HPF. Drawings of the major cell layer in each cortical field were made from an equally-spaced series of transverse Nissl-stained sections, enlarged 82 times, and traced onto appropriately thick sheets of foam rubber. The foam rubber representations of the HPF were glued together to create a solid model, and then the lines between foam rubber sheets were traced onto clear polyethylene film stretched over the surface of the model. When the film was laid out on a table the surface of the model was flattened and the borders of the various HPF fields were obvious, as was the shape of the series of transverse histological sections through the original HPF, to a first order of approximation (Fig. 6).

Since the original HPF flatmap was published over two decades ago, several useful refinements have become obvious, and they have been incorporated into the revised version presented in Fig. 6. First and foremost, the dentate gyrus has been connected to the rest of the map in a topologically accurate way (with the 'lateral' blade bordering field CA3), rather than being shown as an isolated area. This is justified because the dentate gyrus develops, of course, from a continuous sheet of pallium, and the new map provides a better representation of pathways that enter and leave the gyrus from field CA3. Second, the topology of the ventral (temporal) end of the subicular complex was drawn more accurately, based on the brain used for our atlas [134]. Third, an obvious ventral zone of the medial entorhinal area was added [16], and the rostroventral tip of the lateral entorhinal area was extended rostrally [134]. And fourth, the tiny fasciola cinerea, a very poorly differentiated region of the embryonic hippocampus, was added to the map.

Two other helpful features have also been added to the map. One is the approximate location of a selected series of levels from our atlas of the rat brain (Fig. 6, shown in blue), and the other is the approximate location of possible functional domains in field CA1/subiculum (Fig. 6, shown in green), as suggested by our earlier studies of hippocampo-septo-hypothalamic pathways [112,114]. These domains are meant to represent the main focus of neurons with a projection to a specific region of the lateral septal complex that in turn has bidirectional connections with a particular structure(s) in the hypothalamus. This is not to say that a diminishing gradient of neurons with similar projections is not found outside a particular domain, or conversely that relatively small numbers of neurons with projections to other parts of the lateral septal complex (from adjacent domains) are not found within that domain.

We shall now discuss how our PHAL analysis clarifies the organizing principles of amygdalo-hippocampal projections, following the same basic approach that was used for direct amygdalo-hypothalamic projections in Sections 2.3–2.6. How these projections are related to specific parts of the hypothalamus via direct and hippocampo-septal pathways will be discussed in Section 4.

3.2. Projections from the frontotemporal system

Recall that the lateral and anterior basolateral nuclei of the amygdala receive their most dense cortical inputs from temporal and orbitofrontal association areas (Fig. 3).

3.2.1. From the lateral nucleus

Three PHAL injections were placed in the lateral nucleus; two were restricted to ventromedial regions and one to ventrolateral regions. The dorsal tip of the lateral nucleus was not labeled in any of the experiments. The two injections involving the ventromedial lateral nucleus labeled an essentially identical pattern of projections to the HPF, and experiment 10 will be described in detail because labeled neurons appeared to be restricted entirely to the lateral nucleus (Figs. 7–9). Interestingly, the experiment involving ventrolateral regions of the lateral nucleus (experiment 89) displayed a striking lack of projections to the hippocampus proper and subiculum, although inputs to the entorhinal and perirhinal areas and to the parasubiculum were similar to those labeled by injections involving ventromedial regions of the nucleus.

3.2.1.1. To the entorhinal and adjacent areas. Ventromedial regions of the lateral nucleus provide a substantial input to the lateral entorhinal area — specifically to a topologically medial region in approximately the middle third of the area as measured along the dorsoventral axis (Fig. 7) — although some fibers are also present in the rest of the lateral entorhinal area (Figs. 7 and 9). The caudal half of layer 3 is most densely innervated, although there is a light input to layers 4–6 and sparse fibers in layers 1 and 2 (Figs. 8 and 9). Krettek and Price [72] first demonstrated this massive input to layer 3, which

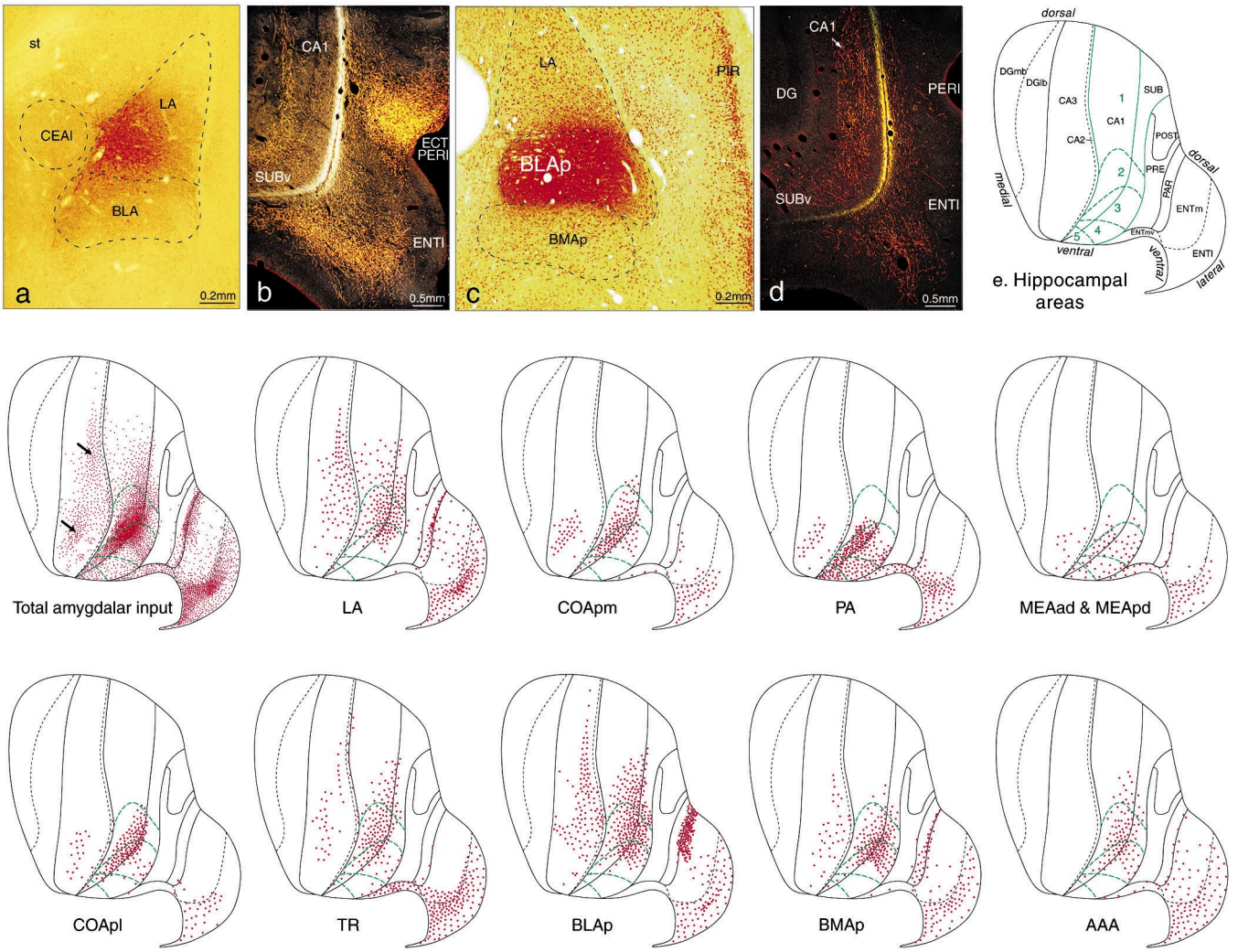


Fig. 7. Overall distribution pattern of amygdalar inputs to the HPF illustrated on a flatmap. (a,b) Photomicrographs of transverse sections through the right hemisphere in experiment 10 to show the location of a PHAL injection site in the lateral nucleus (a; brightfield), and the resulting axonal labeling in the HPF (b; darkfield). (c,d) Photomicrographs of transverse sections through the right hemisphere in experiment 87 to show the location of a PHAL injection site in the posterior basolateral nucleus (c; brightfield), and the resulting axonal labeling in the HPF (d; darkfield). (e) Major cortical fields of the flattened HPF, along with postulated functional domains in hippocampal field CA1 and the subiculum (see Fig. 6 for details). Bottom two rows. Total amygdalar input to the HPF (red dots; arrows indicate apparent dorsal and ventral terminal patches in field CA3), along with pattern of input (red dots) from individual cell groups, as indicated by their abbreviations.

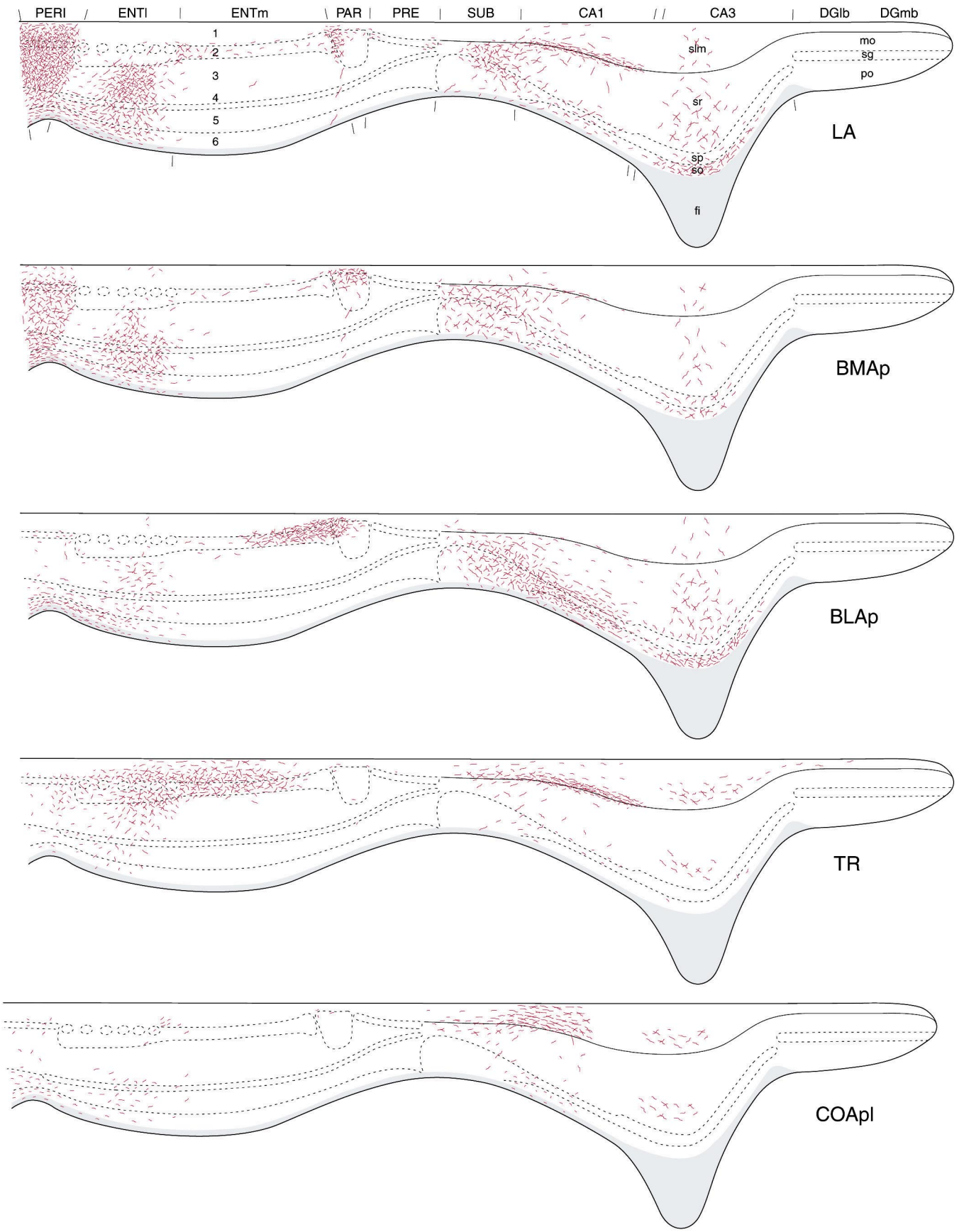


Fig. 8. Summary of laminar distribution of amygdalar inputs (red) to the HPF. The location of this hypothetical cut through the HPF flatmap is shown as dashed line z,z in Fig. 6. Basic laminar pattern from individual amygdalar cell groups are indicated; see text for details.

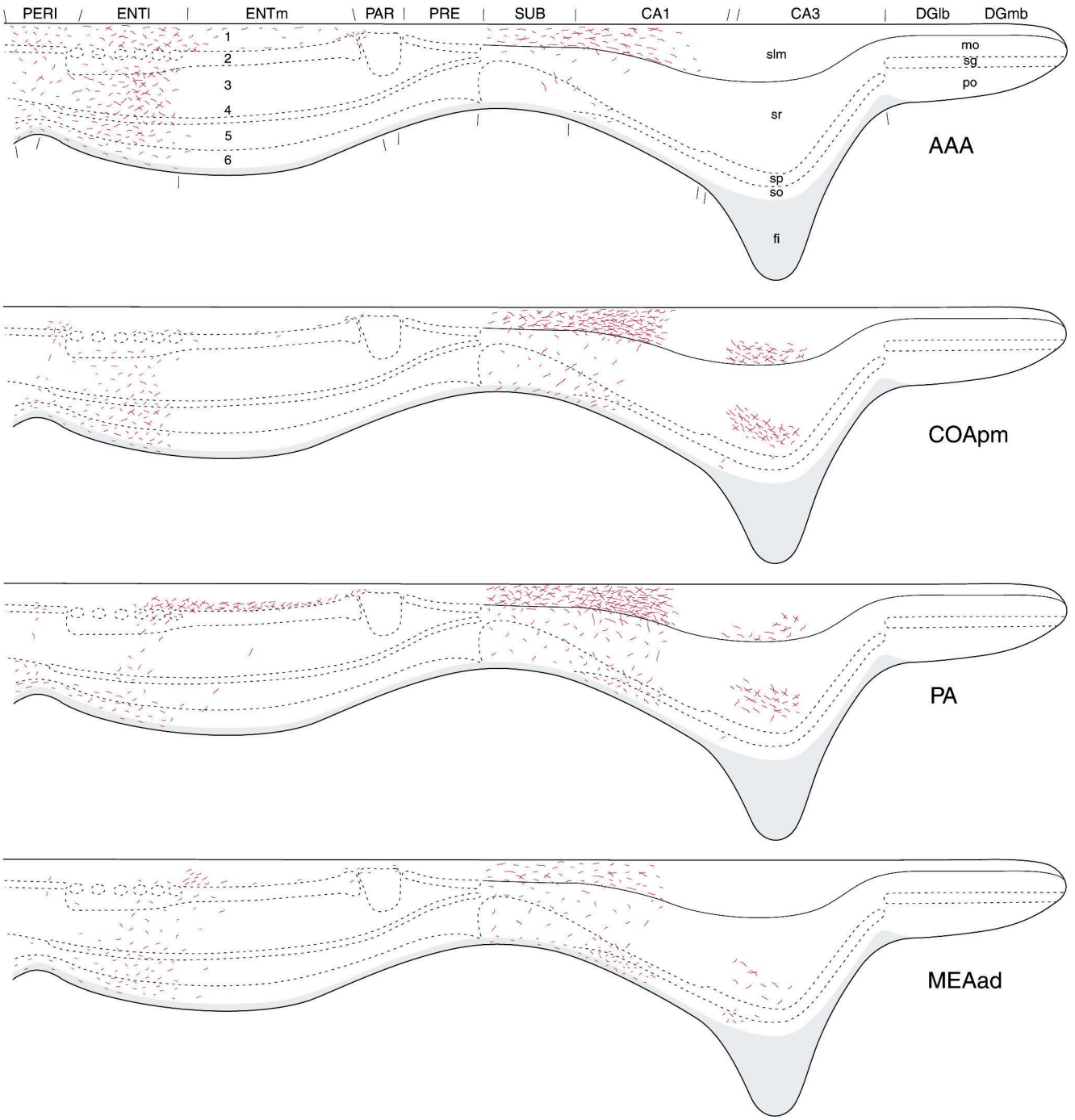


Fig. 8. (*continued*)

is corroborated by evidence that after HRP injections in ventral regions of the lateral entorhinal area the greatest number of retrogradely labeled neurons are found caudally in the lateral amygdalar nucleus [8]. In their recent PHAL analysis, Pitkänin and colleagues [108] described a projection to the deep part of layer 3, and some fibers in layers 5 and 6, of rostromedial regions of the 'ventral intermediate entorhinal subfield,' which corresponds to the medial half of the lateral entorhinal area as defined here.

Ventromedial regions of the lateral nucleus also appear to innervate the dorsal half or so of the medial entorhinal area (Fig. 7), where there is a light input to layer 2 and a sparse input to the deep part of layer 1 (Figs. 8 and 9F).

The lateral nucleus also sends exceptionally dense inputs to the perirhinal and ectorhinal areas (Brodmann's areas 35 and 36, respectively), which are dorsally adjacent to the entorhinal area itself (Figs. 7–9). PHAL-labeled axons travel from the lateral nucleus through the extreme capsule

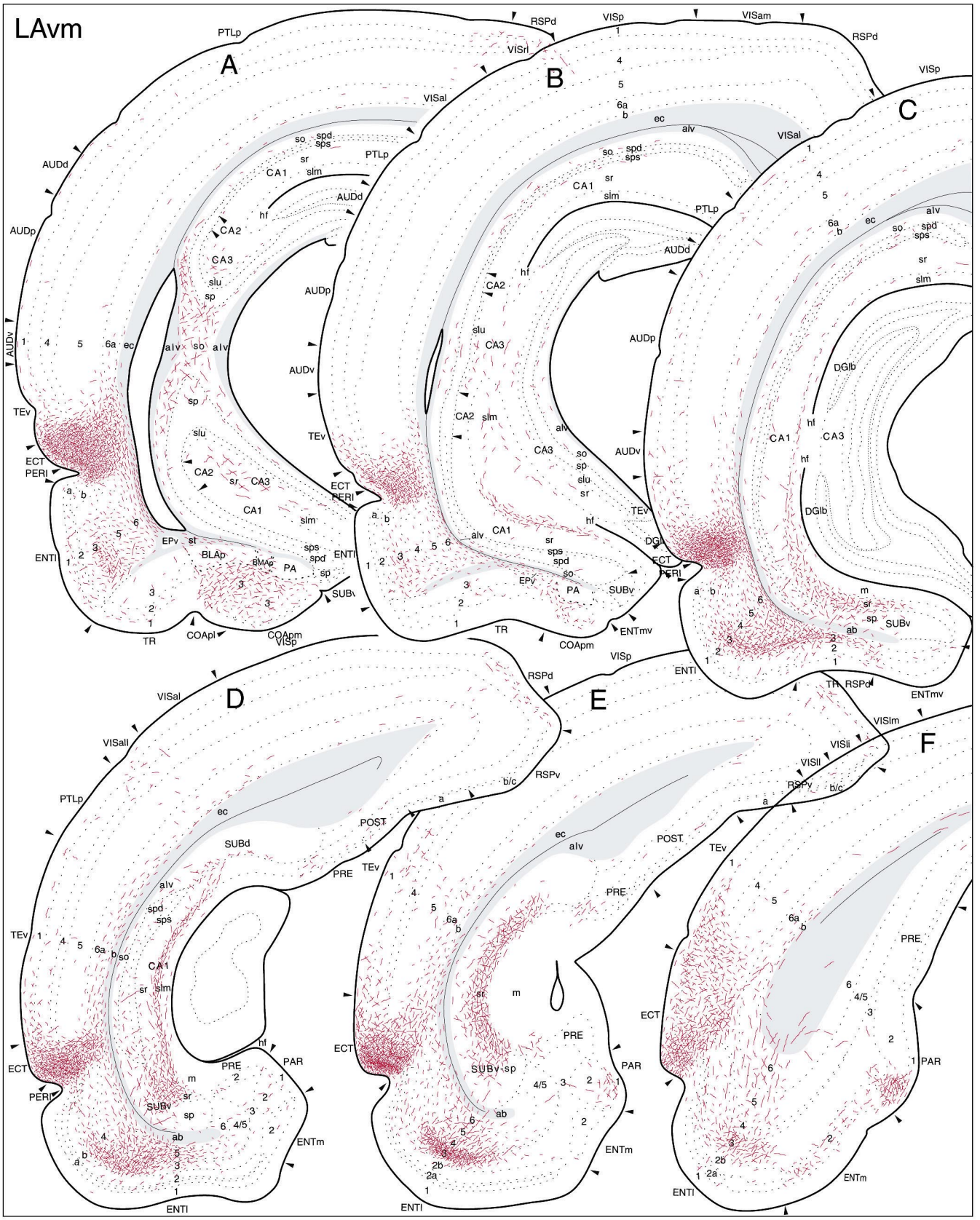


Fig. 9. Distribution of PHAL-labeled projections (red) from ventromedial regions of the lateral amygdalar nucleus (LAvm) to the HPF. The results of experiment 10 were plotted onto a series of rat brain atlas templates [134], arranged from rostral (A) to caudal (F).

and layer 6 to generate an extraordinarily dense plexus of terminals in the deep part of layer 1, and in layers 2 and 3; a dense input to layer 5; and moderately dense inputs to layer 6 and the superficial part of layer 1. This is the most substantial projection from the amygdala to other regions of the cerebral hemisphere that we have observed. In contrast, ventromedial regions of the lateral nucleus send only a few axons to the postpiriform transition area — the cortical field rostroventrally adjacent to the lateral entorhinal area — except very caudally, where there is a moderate to light input to the deep part of layer 3, and to layer 4 (Fig. 9C).

In their classic autoradiographic study Krettek and Price [72] found silver grains over an area that corresponds to our postpiriform transition and perirhinal areas after a large injection into the lateral and basolateral nuclei. Our results suggest an extraordinarily dense projection to the perirhinal and ectorhinal areas — and a very light input to the postpiriform transition area — from the lateral nucleus, whereas the reverse is true for the posterior basolateral nucleus (see Section 3.4.2). This is consistent with earlier retrograde tracer experiments where injections in the perirhinal area label many neurons in the lateral and posterior basomedial nuclei, but only a few neurons in the posterior basolateral nucleus of the rat [88] and cat [118].

For the sake of completeness, we should mention that the lateral nucleus also sends light projections to ventral temporal association areas (TEv) dorsal to the ectorhinal area, mainly to layers 1–3 and 6 (Fig. 9A–C), and to all layers of the anterior laterolateral visual area (Fig. 9D). Some labeled axons with terminal boutons are also present in layers 1, 2, and 6 of the dorsal, ventral, and posterior auditory areas (Fig. 9A–C), and in the posterior parietal association area (Fig. 9B–D). Finally, axons-of-passage with occasional boutons-of-passage travel through layer 6 of the dorsal visual area to reach the dorsal part of the retrosplenial area, where they provide light to moderate inputs centered in the deep part of layer 1, and in layer 2, although scattered fibers are present in all of the other layers as well.

3.2.1.2. To Ammon's horn. The ventromedial lateral nucleus innervates a rather broad expanse of fields CA3 and CA1, at least in the ventral two-thirds or so of their longitudinal extent (Fig. 7). In field CA3 labeled axons are found relatively densely in the stratum oriens, relatively moderately in the stratum radiatum and stratum lacunosum-moleculare, and very lightly in the pyramidal layer (Fig. 9A and B). These axons appear to branch very little, typically one long branch with a terminal bouton is observed, and they generate few boutons-of-passage.

The most dense terminal plexus in field CA1 is found laterally (topologically), adjacent to the subiculum, about midway along the dorsoventral axis in domains 2 and 3 (Fig. 7). The deepest region of the stratum lacunosum-moleculare, including its border with the stratum radiatum, is very densely innervated, whereas the stratum oriens and pyramidal layer receive a light input — which becomes more dense in the ventral tip of field CA1, in the region bordering the ventral subiculum (Figs. 8 and 9). Some labeled fibers were also observed in adjacent regions of field CA2.

Clear projections from the lateral nucleus to fields CA2 and 3 have not been reported in earlier anterograde tracing experiments [72,108]. Krettek and Price [72] did observe silver grains over the stratum lacunosum-moleculare in the ventral tip of field CA1 after an injection involving the lateral and basolateral nuclei, and Pitkänen and colleagues [108] described ammonic projections of the lateral nucleus as restricted to the ventral third of field CA1.

3.2.1.3. To the subicular complex. In a recent PHAL study Pitkänen and colleagues [108] described a light input to the molecular layer, and a few terminals in the cell layer, of the ventral tip of the subiculum from the lateral nucleus. However, we observed a much more dense and extensive terminal field, centered in domain 2 but extending well into adjacent regions of domains 1 and 3 (Fig. 7). These axons are dense in the stratum radiatum and tend to avoid the molecular layer proper, and they are also dense in the superficial half of the pyramidal layer, and light in the deep half of this layer (Figs. 8 and 9).

In addition, the lateral nucleus sends a distinct projection to deep layer 1 and layer 2 of a narrow, topologically lateral zone of the parasubiculum adjacent to the medial entorhinal area (Fig. 7), confirming the recent findings of Pitkänen and colleagues [108].

After a PHAL injection centered in ventrolateral rather than ventromedial regions of the lateral nucleus, the same innervation patterns in the entorhinal, perirhinal, and ectorhinal areas and in the parasubiculum were labeled. However, only sparse labeling was observed in the subiculum, and none was observed in Ammon's horn.

3.2.2. From the anterior basolateral nucleus

Five PHAL injections were centered in this nucleus: two were in the rostral half, one was in the caudal third, and two spread throughout much of the nucleus. In all experiments there was very little indication of labeled projections to the HPF, other than a very light input to the most dorsal region (one-eighth or so) of the lateral entorhinal area, and both dorsal and ventral regions of the subiculum and adjacent field CA1 — regions only sparsely innervated (except for the ventral subiculum and adjacent field CA1) by other amygdalar cell groups. These results agree with the recent analysis of Pitkänen and colleagues [108].

3.3. Projections from the autonomic system

None of our injections in any part of the central nucleus labeled a projection to the HPF or surrounding cortical

areas, in agreement with previous anatomical [72] and physiological [52] evidence.

3.4. Projections from the main olfactory system

Our suggested pairing of main olfactory cortical with claustral/subplate cell groups that are associated with the amygdala is illustrated in Figs. 1–3.

3.4.1. From the posterior basomedial nucleus and piriform-amygdalar area

Our analysis of projections from the posterior basomedial (accessory basal) nucleus has been published elsewhere [106], so the results will just be summarized here, and for the sake of comparison newly illustrated on the flatmap (Fig. 7), schematic cross section (Fig. 8), and atlas levels (Fig. 10).

3.4.1.1. To the entorhinal and adjacent areas. Projections to the HPF from the posterior basomedial nucleus are strikingly similar to those just described for the lateral nucleus, although somewhat lighter (Fig. 7). Thus, most terminals in the entorhinal area are in topologically medial regions of the lateral part, where they are moderately dense in layers 3–5, and light in layer 6. The posterior basomedial nucleus only innervates the deep zone of layer 3, whereas the lateral nucleus innervates its entire thickness. The ventral half of the medial entorhinal area contains only scattered axons from the posterior basomedial nucleus.

As with the lateral nucleus, the posterior basomedial nucleus also densely innervates the perirhinal and ectorhinal areas, and its only input to the postpiriform transition area appears to be restricted to caudal regions of layer 6. In the perirhinal area there are dense terminal fields in deep layer 1, and layers 2, 3, and 5; and moderate to light terminal fields in superficial layer 1 and layer 6. In addition, the posterior basomedial nucleus sends a few axons to layers 1, 5, and 6 of ventral temporal association areas (TEv); to dorsal, ventral, and posterior auditory areas; to the posterior parietal region; and to layer 2 of the anterolateral visual area.

After retrograde tracer injections in the lateral entorhinal area labeled neurons were found in the region of what we call the posterior basomedial nucleus [8], as they were after such injections in the perirhinal area of the rat [88] and cat [118]. Krettek and Price [72] did not detect cortical projections from the posterior basomedial nucleus, although they have been reported in a recent PHAL study [108].

3.4.1.2. To Ammon's horn. Again, the distribution of projections here from the lateral and posterior basomedial nuclei are quite similar, although less dense from the latter. In ventral field CA1 there is a moderate input to deep regions of the stratum lacunosum-moleculare, and a lighter input to the stratum radiatum, stratum oriens, and pyramidal layer. In ventral field CA3 there is a moderate input to the stratum oriens and stratum lacunosum-moleculare.

In one respect our experiments confirm those of Pitkänen and colleagues [108], who reported a moderate input to the stratum lacunosum-moleculare of the ventral two-thirds of field CA1, and a light input to the pyramidal layer of the most temporal and distal regions of field CA1 from an injection in their magnocellular division of the accessory basal nucleus, which corresponds approximately to the rostral tip of our posterior basomedial nucleus. However, they reported terminals only in the temporal third of field CA1 and ventral tip of the subiculum after injections in the center of the accessory basal/posterior basomedial nucleus, and none of their injections in this region labeled axons in field CA3 (or CA2).

3.4.1.3. To the subicular complex. As with the lateral nucleus, the posterior basomedial nucleus projects densely to the stratum radiatum, and moderately to the pyramidal layer of the subiculum, especially in domains 2 and 3. Pitkänen and colleagues [108] reported light projections mainly to deep regions of the molecular layer, and a few axons in superficial regions of the pyramidal layer of the ventral third of the subiculum. The input to the parasubiculum from the posterior basomedial nucleus is very similar to that described above for the lateral nucleus, in agreement with Pitkänen and colleagues [108].

The piriform-amygdalar area appears to be the region of main olfactory cortex most closely associated with the posterior basomedial nucleus, and its projection to the HPF appears to be essentially identical to that from the posterior basomedial nucleus, but much lighter (not illustrated).

3.4.2. From the posterior basolateral nucleus

Although the posterior basolateral nucleus and postpiriform transition area are closely related (Figs. 1–3), their HPF projections will be described separately because they are somewhat complex. Four PHAL injections were centered in the posterior basolateral nucleus, and the projections from experiment 87 will be described in detail because they were typical of those observed in the other three (Figs. 7, 8, and 11).

3.4.2.1. To the entorhinal and adjacent areas. The posterior basolateral nucleus innervates exactly the same region of the lateral entorhinal area as the lateral and posterior basomedial nuclei, although considerably more lightly, which is corroborated by earlier retrograde tracer work [8].

The posterior basolateral nucleus also sends a heavy, circumscribed projection to a region of the dorsal medial entorhinal area. This projection ends in deep layer 1 and layer 2, where neurons generate perforant path fibers to the dorsal dentate gyrus and Ammon's horn [131]. This pathway has not been reported earlier with anatomical methods, but lesions of the basolateral nucleus attenuate LTP in medial perforant path-dentate gyrus granule cell

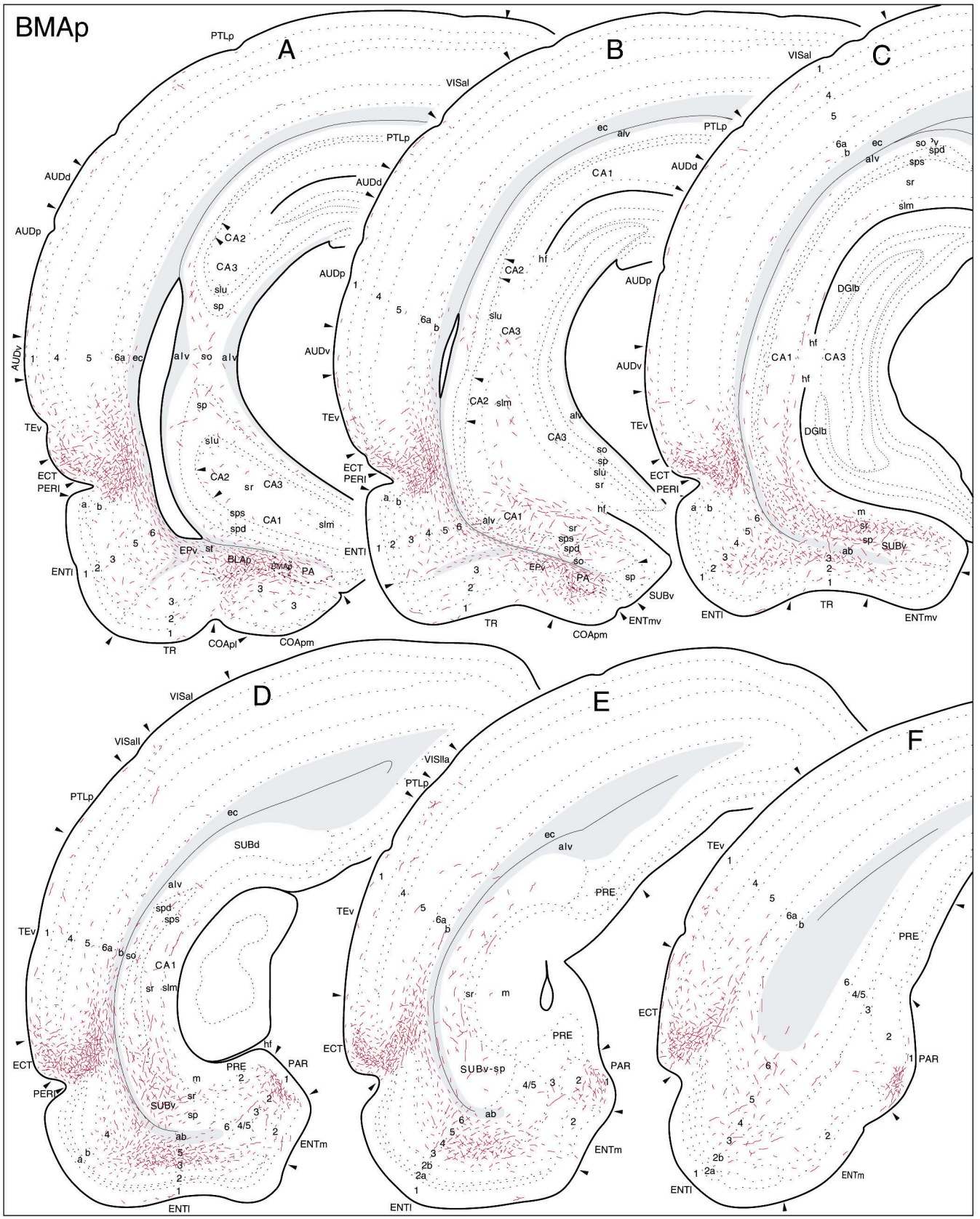


Fig. 10. Distribution of PHAL-labeled projections (red) from the posterior basomedial nucleus to the HPF. The results of experiment 28 were plotted onto a series of rat brain atlas templates [134], arranged from rostral (A) to caudal (F).

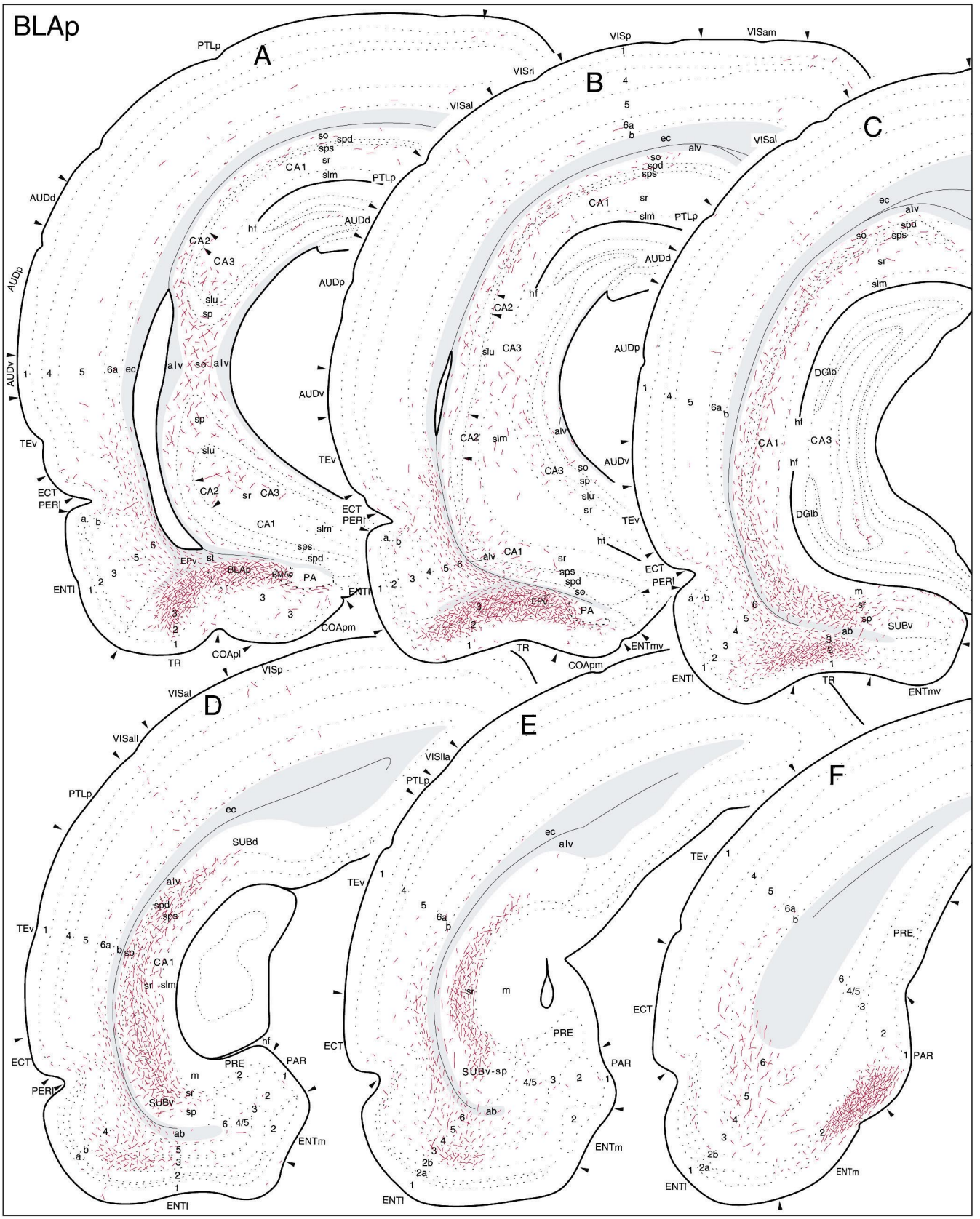


Fig. 11. Distribution of PHAL-labeled projections (red) from the posterior basolateral nucleus to the HPF. The results of experiment 87 were plotted onto a series of rat brain atlas templates [134], arranged from rostral (A) to caudal (F).

synapses [52]. Although a direct projection from the basolateral nucleus to the dentate gyrus has been suggested on electrophysiological grounds [53,54], there is no anatomical evidence to support its existence.

The posterior basolateral nucleus also sends a very dense input to layer 3 of the postpiriform transition area, as well as a moderate input to layer 2, and a light input to the molecular layer. As mentioned in Section 3.2.1, Krettek and Price [72] found silver grains over what corresponds to our postpiriform transition and perirhinal areas after large amino acid injections that included the lateral and basolateral nuclei. Our results indicate that the input to the postpiriform transition area comes mainly from the posterior basolateral nucleus whereas the input to the perirhinal area comes mainly from the lateral nucleus (Section 3.2.1).

3.4.2.2. To Ammon's horn. The areal distribution of terminals from the posterior basolateral nucleus in field CA3 is quite unusual. Examination of the total amygdalar input suggests that there are relatively discrete dorsal and ventral terminal regions in field CA3, and the posterior basolateral nucleus would appear to innervate both (Fig. 7). Inputs to the stratum oriens are relatively dense, those to the stratum oriens relatively moderate, and those to the pyramidal layer relatively light.

The areal distribution of terminals in field CA1 is rather similar to that from amygdalar cell groups already described. It is centered in topologically lateral regions of domain 3, but spreads to adjacent regions of domains 1 and 3, as well as to topologically more medial regions of the field (Fig. 7). The bulk of this projection is centered in the stratum oriens, pyramidal layer, and stratum radiatum, with very little input to the stratum lacunosum-moleculare. This pattern is complementary to the one generated by the lateral and posterior basomedial nuclei (Fig. 8). Axons from the posterior basolateral nucleus in field CA1 display boutons-of-passage and modest branching, which becomes especially infrequent dorsally.

Pitkänen and colleagues [108] reported a much less extensive input to Ammon's horn from the posterior basolateral/parvicellular basal nucleus.

3.4.2.3. To the subicular complex. The areal distribution of subicular inputs from the posterior basolateral nucleus are virtually the same as those from the lateral and posterior basomedial nuclei. There is a dense input to the stratum radiatum and deep half of the pyramidal layer and a light input to the superficial half of the pyramidal layer — the molecular layer appears to be avoided. We cannot explain why Pitkänen and colleagues [108] observed a heavy input directed to superficial regions of the pyramidal layer, although it is entirely possible that the posterior basolateral/parvicellular basal nucleus is more heterogeneous than currently appreciated.

The posterior basolateral nucleus also projects to a dense, longitudinally narrow zone of terminals in the dorsal parasubiculum that is continuous with the terminal field in the dorsal medial entorhinal area mentioned earlier in this section (Figs. 7, 8, and 11) (also see Ref. [108]).

3.4.3. From the postpiriform transition area

Although this region has occasionally been thought of as part of the lateral entorhinal area [74], recent evidence shows that it does not project significantly to the dentate gyrus through the perforant path (Ref. [127] and present results). We have obtained three PHAL experiments with labeled neurons restricted entirely to the postpiriform transition area, and will describe number 59, with an injection centered in layer 2 (Fig. 12B), because it labeled projections to the HPF most densely (Figs. 7, 8, and 12).

3.4.3.1. To the entorhinal and adjacent areas. First we should note that the postpiriform transition area generates local projections — there is a very dense plexus in the deep molecular layer and a light plexus in the superficial molecular layer, a dense plexus in layer 2, and a moderate plexus in layer 3 throughout the rest of the area. Next, there is a widespread projection to essentially the entire lateral entorhinal area, and to ventral regions of the medial entorhinal area (Fig. 7). These projections to the entorhinal area are concentrated in the deep molecular layer and in layers 2 and 3, which generate perforant path projections to the dentate gyrus and field CA1, respectively [131].

Like other amygdalar cell groups associated with the main and accessory olfactory systems, the postpiriform transition area projects lightly to the deep molecular layer, and to layers 2 and 3 of the perirhinal area, especially ventrally.

3.4.3.2. To Ammon's horn. Postpiriform transition area fibers reach the hippocampus proper via both dorsal and ventral routes. From the injection site, labeled axons extend dorsally through ventral regions of the lateral entorhinal area and then cross the angular bundle to reach field CA1. The other small group of axons travels ventrally through the molecular layer of the ventral zone of the medial entorhinal area and then through the ventral subiculum.

Within field CA3, there appear to be two light terminal fields, in the dorsal and ventral patches described in the previous section for posterior basolateral inputs. In experiment 59 (where the injection is centered in layer 2; Fig. 12B) these fibers are concentrated in the stratum lacunosum-moleculare and stratum radiatum. However, in experiment 77, where the injection is centered caudomedially in layer 3 (see Fig. 17 in Ref. [33]), there is clear labeling in the stratum oriens, as well as in the stratum lacunosum-moleculare and stratum radiatum.

Projections to field CA1 from the postpiriform transition area are very similar in areal distribution to those already described for the lateral and posterior basolateral nuclei — they are centered in domain 2 and adjacent regions of

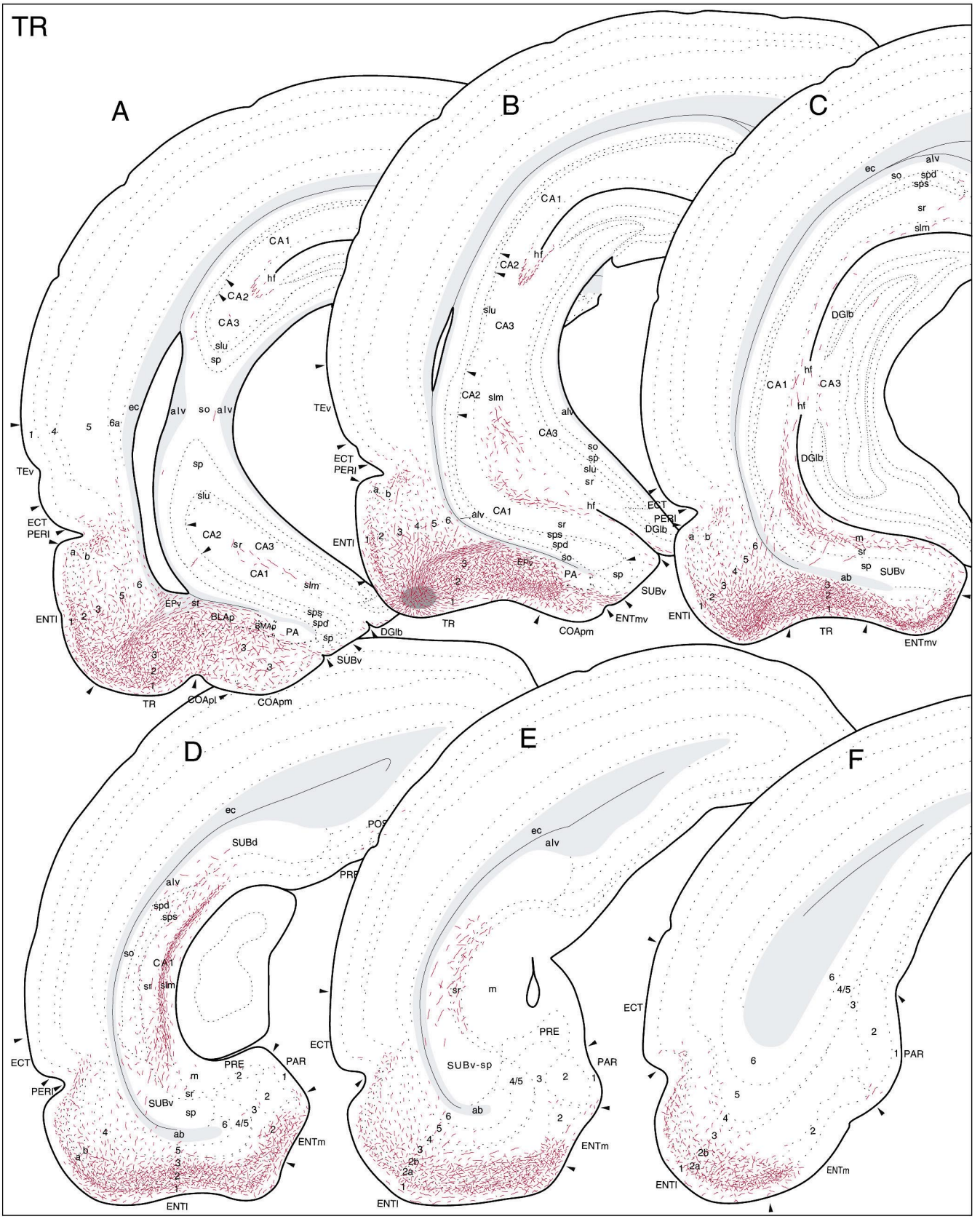


Fig. 12. Distribution of PHAL-labeled projections (red) from the postpiriform transition area to the HPF. The results of experiment 59 were plotted onto a series of rat brain atlas templates [134], arranged from rostral (A) to caudal (F). The center of the injection site is show as a gray oval in section B.

domains 1 and 3. This projection is centered in the stratum lacunosum (Figs. 8 and 12).

3.4.3.3. To the subicular complex. Rostrally the subicular molecular layer receives a light input from the postpiriform transition area (Fig. 12C) whereas more caudally the stratum radiatum and pyramidal layer are innervated (Fig. 12D and E). Only a few scattered fibers were observed in the ventral parasubiculum near the medial entorhinal area.

3.4.4. From the anterior basomedial and anterior cortical nuclei

Their projections have been described in detail elsewhere [106]. The anterior basomedial nucleus sends a light input to the molecular layer of the lateral entorhinal area, and the anterior cortical nucleus sends a very light input to the entorhinal and perirhinal areas.

3.4.5. From the posterolateral cortical nucleus

Although the total output of this cell group has been described elsewhere [16], for the sake of comparison it is useful to describe HPF inputs in more detail, especially graphically (Figs. 7, 8, and 13).

3.4.5.1. To the entorhinal and adjacent areas. The posterolateral cortical nucleus sends a very light input to deep layer 3 and layers 4–6 of the ventral lateral entorhinal area (Figs. 7 and 8). Medial regions of layer 1 in the postpiriform transition area also receive a very light input, as do all layers of the perirhinal and ectorhinal areas.

3.4.5.2. To Ammon's horn. The posterolateral cortical nucleus sends a very light input to the same regions of the hippocampus proper as the various components of the accessory olfactory system (Section 3.5). Thus it innervates the stratum lacunosum in a ventral patch of field CA3, and it innervates more densely a region centered in the topologically lateral half of field CA1 domains 2 and 3 (Fig. 7), especially in the stratum lacunosum (Figs. 8 and 13).

3.4.5.3. To the subicular complex. There is a light input to the stratum radiatum and pyramidal layer of subicular domain 3.

3.4.6. From the anterior amygdalar area

In three experiments the PHAL injection site was centered in this area, and in experiment 69 there were very few labeled neurons outside its rather fuzzy borders (see Figs. 7, 8, and 14).

3.4.6.1. To the entorhinal and adjacent areas. The anterior amygdalar area sends at least a very light input to the entire lateral entorhinal area, although it is more dense ventrally, where it is concentrated moderately in layers 1 and 3, lightly in layers 4–6, and sparsely in layer 2. Note that there are terminals throughout the thickness of the molecular layer (Figs. 8 and 14).

In the postpiriform transition area, anterior amygdalar area inputs end densely in medial regions of layer 1, and moderately in the rest of layer 1, and there is a light input to layers 2 and 3 of the entire transition area. There are some apparent fibers-of-passage in layer 3, which thus appears to contain a slightly more dense input.

Finally, the anterior amygdalar area projects substantially to temporal association areas dorsal to the entorhinal area. Thus, ventral regions of the perirhinal area receive a dense input to layer 1, a moderate input to layers 2 and 3, and a light input to layers 5 and 6. More dorsal regions of the perirhinal area receive a very light input from the anterior amygdalar area, as do the ectorhinal and ventral temporal association areas, especially caudally (Fig. 14A–F).

3.4.6.2. To Ammon's horn. Our injections centered in the anterior amygdalar area did not label a significant input to field CA3. However, there is a projection centered in domains 2 and 3 of field CA1, where there are light to moderate numbers of fibers and terminals in the stratum lacunosum-moleculare, and scattered fibers in the pyramidal layer and the stratum radiatum and stratum oriens (Figs. 7, 8, and 14).

3.4.6.3. To the subicular complex. There is also a light to moderate input to the molecular layer of the subiculum, in the region just adjacent to the terminal plexus in field CA1 (Figs. 7, 8, and 14). Large HRP injections in the ventral HPF retrogradely label neurons in the anterior amygdalar area [158].

3.4.7. From the nucleus of the lateral olfactory tract and intercalated nuclei

Although we did not obtain any PHAL injections restricted to these cell groups, there is no evidence in the previous neuroanatomical literature to suggest that they project to the HPF (e.g., [31,72,82]).

3.5. Projections from the pheromonal system

Overall, amygdalar cell groups associated with the accessory olfactory system tend to innervate mainly the ventral lateral entorhinal area, a terminal field in the ventral subiculum/field CA1, and a ventral patch in field CA3.

3.5.1. From the posteromedial cortical nucleus

This is the only cortical field projected upon significantly by the accessory olfactory bulb. Its overall projections have been described elsewhere [16]; here we shall provide a more detailed account of its input to the HPF, especially graphically (Figs. 7, 8, and 15). They are very

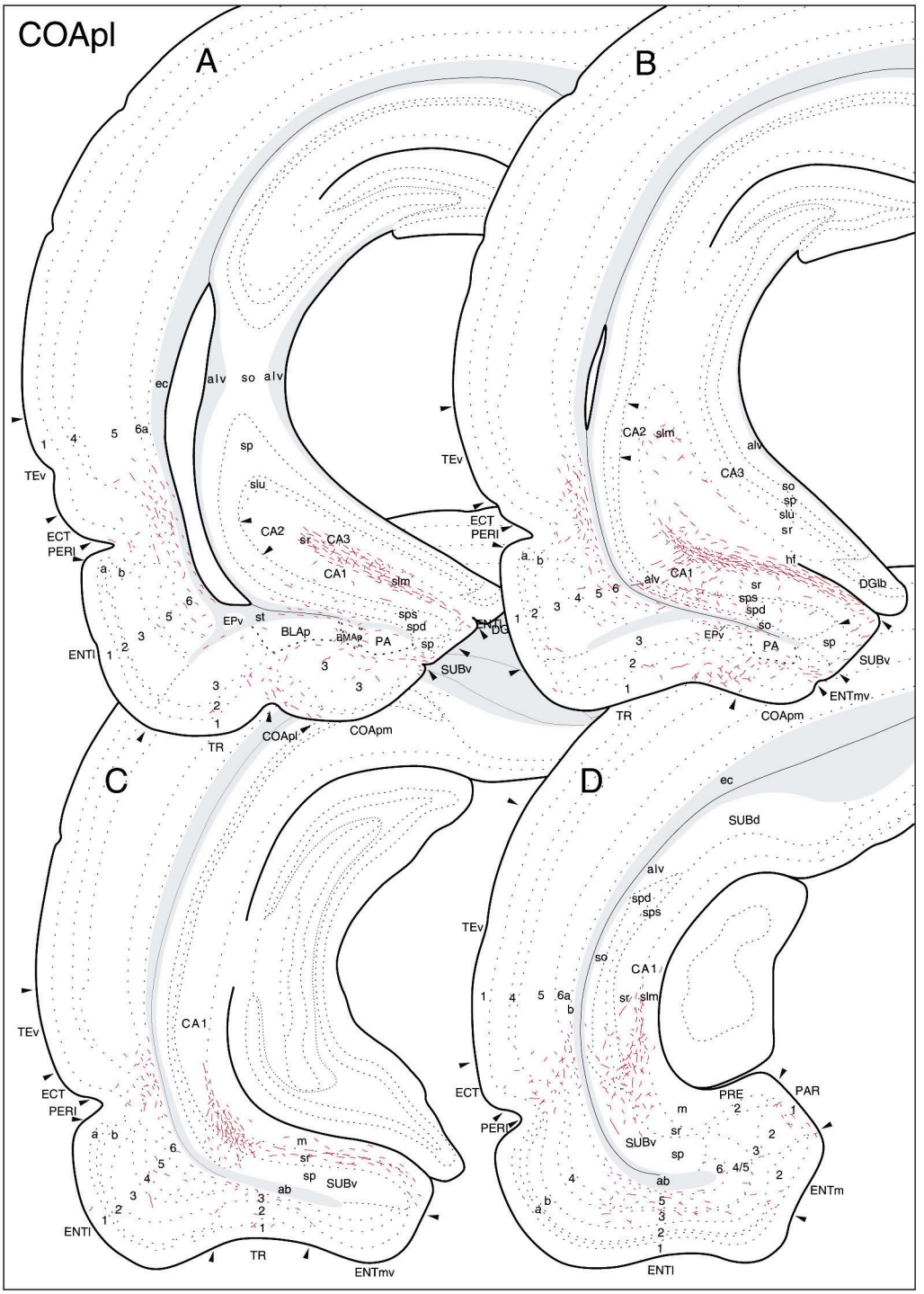


Fig. 13. Distribution of PHAL-labeled projections (red) from the posterolateral cortical nucleus to the HPF. The results of experiment POCL2 were plotted onto a series of rat brain atlas templates [134], arranged from rostral (A) to caudal (D).

similar to those described above (Section 3.4.5) for the posterolateral cortical nucleus.

3.5.1.1. To the entorhinal and adjacent areas. Most posteromedial cortical nucleus input to the entorhinal area is directed toward ventral regions of the lateral part, where there is a moderate innervation of layers 3–6 and a sparse input to layers 1 and 2. Retrograde tracer experiments with HRP first hinted at this projection [8]. The posteromedial cortical nucleus also projects to the medial third or so of the postpiriform transition area, where there is a relatively dense plexus of fibers in the deep part of the molecular layer, and a lighter plexus in layers 2 and 3 (Fig. 15B–D). Caudally the input to layer 3 becomes a bit more dense

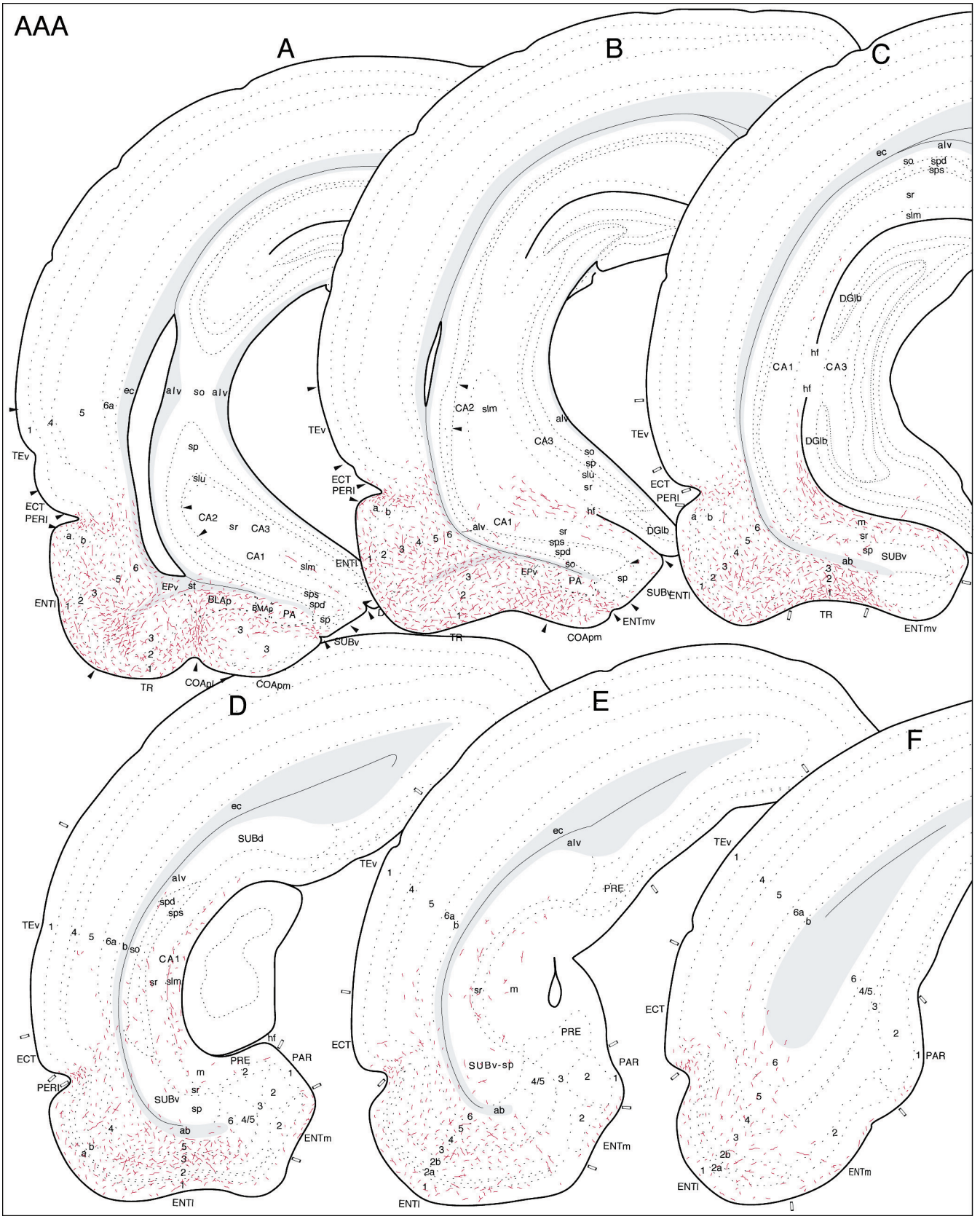


Fig. 14. Distribution of PHAL-labeled projections (red) from the anterior amygdalar area to the HPF. The results of experiment 69 were plotted onto a series of rat brain atlas templates [134], arranged from rostral (A) to caudal (F).

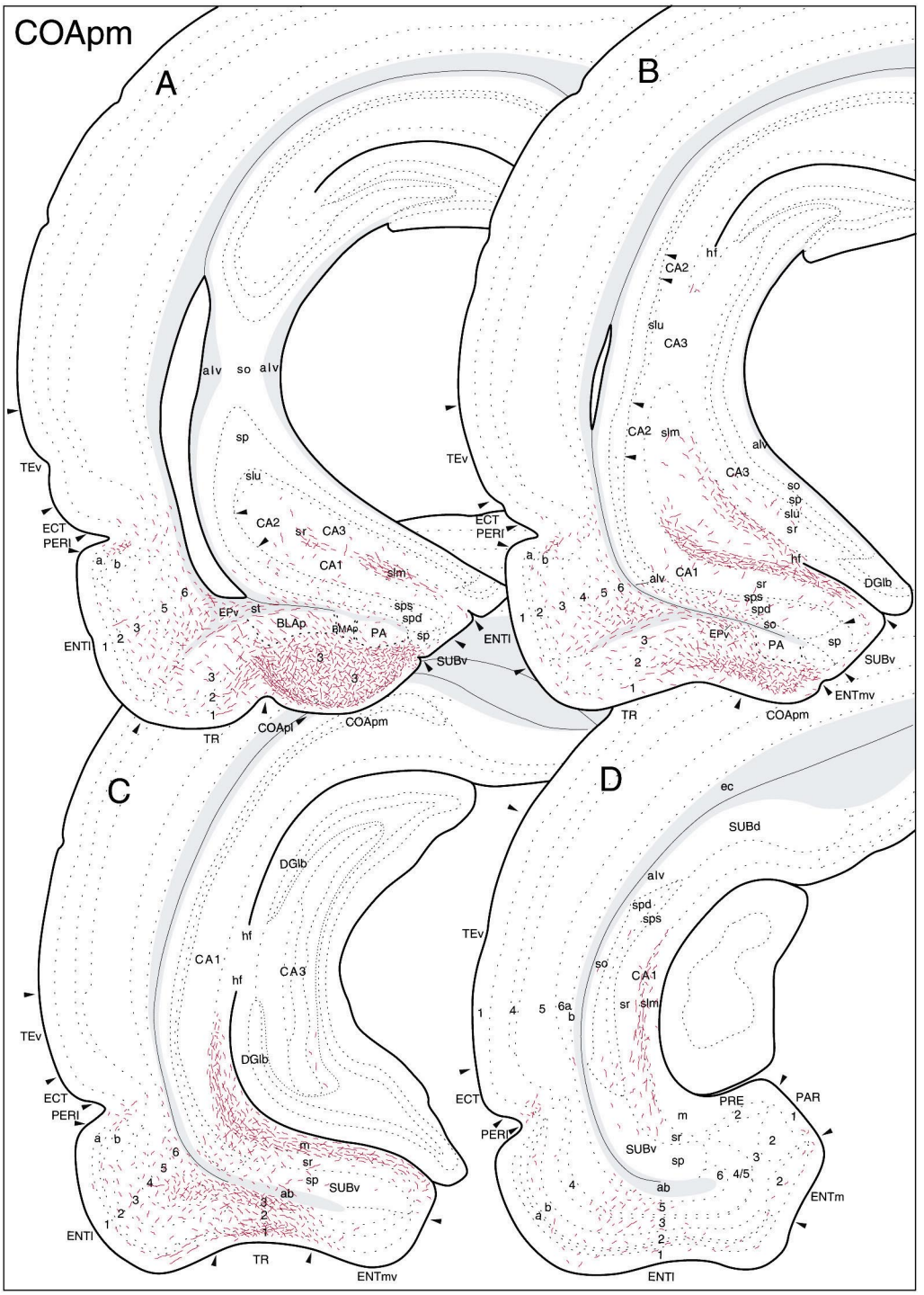


Fig. 15. Distribution of PHAL-labeled projections (red) from the posteromedial cortical nucleus to the HPF. The results of experiment AHZ2 were plotted onto a series of rat brain atlas templates [134], arranged from rostral (A) to caudal (D).

(Fig. 15C), although it contains a number of apparent fibers-of-passage. There is also a light projection from the posteromedial cortical nucleus to ventral regions of the perirhinal area, especially layers 1 and 2.

3.5.1.2. To Ammon's horn and the subiculum. They are essentially the same as those described for the posterolateral cortical nucleus: to a ventral patch in field CA3, and to a region centered in field CA1/subiculum domains 2 and 3 (Figs. 7 and 8). A projection from the posterior cortical nucleus to the molecular layer of fields CA1–3 has been reported in the monkey [123].

3.5.2. From the medial nucleus

The medial nucleus can be thought of as the major striatal component of the accessory olfactory system (Figs. 1–3). Its overall projections have been described elsewhere [19]. Again we shall here provide more detail about its input to the HPF, and for completeness illustrate them in terms of the flatmap (Fig. 7), schematic cross section (Fig. 8), and atlas levels (Fig. 16). Based on an analysis of 20 PHAL injection sites it would appear that all four parts of the medial nucleus that we recognize share qualitatively similar projections to the HPF. Projections from the anterodorsal part will be illustrated because they appear to be somewhat more dense than those from other parts of the nucleus. Overall, the projection from the medial nucleus to

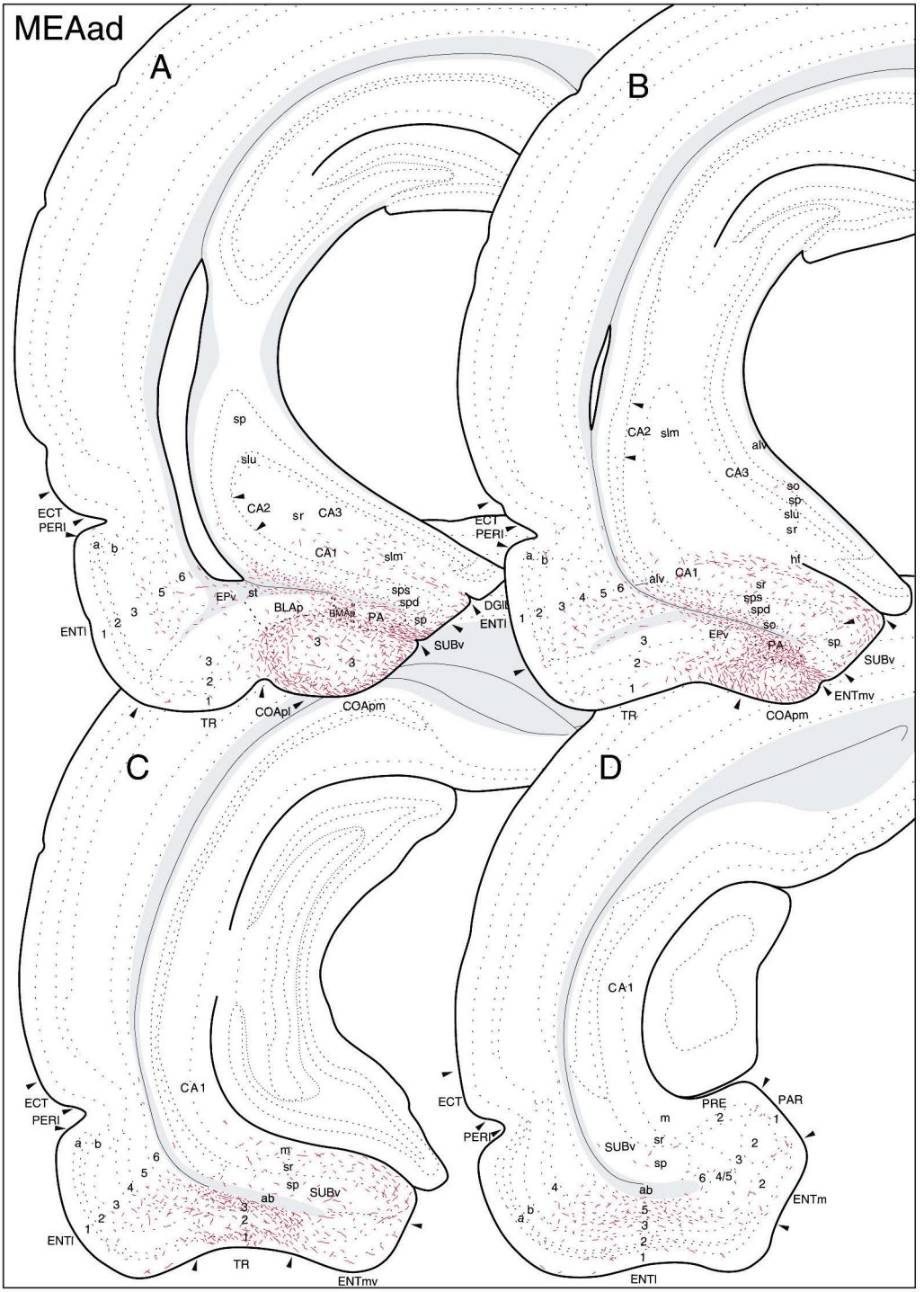


Fig. 16. Distribution of PHAL-labeled projections (red) from the anterodorsal part of the medial nucleus to the HPF. The results of experiment MEA2 were plotted onto a series of rat brain atlas templates [134], arranged from rostral (A) to caudal (D).

the HPF is very similar to that from the posteromedial cortical nucleus, except much lighter.

3.5.2.1. To the entorhinal and adjacent areas. Medial nucleus projections to ventral regions of the entorhinal area (Fig. 7) are concentrated lightly in layers 3–6, and even more lightly in layers 1 and 2 (Figs. 8 and 16). The medial third of the postpiriform transition area, which is also innervated by the posteromedial cortical nucleus, receives an input that is concentrated in layers 1 and 3, and to a lesser extent in layer 2. Only occasional labeled axons were observed in layers 1, 2, and 6 of the perirhinal area.

It is important to point out that all three parts of the accessory olfactory system considered in this section project to the postpiriform transition area, which in turn projects densely to layer 2 of the entorhinal area (Figs. 7, 8, and 12). Obviously, this presents an alternative route for pheromonal influences on the trisynaptic or intrahippocampal circuit, especially to the dentate gyrus (see Section 3.6.1).

3.5.2.2. To Ammon's horn and the subiculum. The ventral patch in field CA3 receives from the medial nucleus a sparse input (Fig. 7) that is concentrated in the stratum radiatum and pyramidal layer (Fig. 8). In addition, domains 3–5 of field CA1/subiculum receive an input from the medial nucleus; this projection is most dense in the stratum lacunosum-moleculare, but scattered fibers are found throughout the other layers as well (Figs. 8 and 16). Vasopressinergic neurons in the medial nucleus have been shown to innervate the ventral subiculum [14]. Finally, the medial nucleus sends a very small number of fibers to the parasubiculum (deep half of layer 1 and superficial regions of layer 2).

3.5.3. From the posterior nucleus

The posterior nucleus lies deep to the posterior cortical nucleus, and may thus form its subplate or claustral part (Figs. 1–3). Its overall output has been described elsewhere [16]. Here we give more detail about its projection to the HPF, and for the sake of completeness and comparison provide graphical summaries on the flatmap (Fig. 7), schematic cross section (Fig. 8), and series of atlas levels (Fig. 17).

3.5.3.1. To the entorhinal and adjacent areas. The posterior nucleus generates a unique input to the entorhinal area in terms of areal distribution: its most dense terminal region is in the ventral third of the entorhinal area, in a continuous region that spans a topologically lateral region of the medial entorhinal area and the adjacent medial region of the lateral entorhinal area (Fig. 7). This projection is centered in very deep regions of the molecular layer and in layer 2a of the lateral entorhinal area (Fig. 8). The rest of the entorhinal area displays only very scattered fibers, except in layer 6, which also contains some apparent fibers-of-passage.

The posterior nucleus also provides a moderate input to layers 1 and 6, and a very light input to layers 2 and 3, of the postpiriform transition area. There is also a light projection to layers 5 and 6, and an even lighter projection to other layers, of the perirhinal and ectorhinal areas.

3.5.3.2. To Ammon's horn and the subiculum. Like both parts of the posterior cortical nucleus, the posterior nucleus innervates a ventral patch in field CA3 (in the stratum lacunosum and stratum radiatum). In field CA1 the posterior nucleus generates a dense, remarkably circumscribed terminal field in the stratum lacunosum-moleculare of domains 3–5. This terminal field spreads into domains 3–5 of the adjacent subiculum, where it is less dense and still confined to the molecular layer (Figs. 7, 8 and 17).

3.6. Conclusions

When amygdalar projections are viewed on a flatmap of the HPF (Fig. 7) the following conclusions are apparent. First, at least 11 amygdalar cell groups project substantially to the HPF. Groups with relatively light or no detectable input to the HPF include the central and intercalated nuclei, the nucleus of the lateral olfactory tract and anterior cortical nucleus, and the anterior basomedial and anterior basolateral nuclei. Second, each amygdalar cell group with a substantial input to the HPF establishes terminal fields in both the entorhinal area and in a circumscribed region spreading through both field CA1 and the subiculum. In addition, all but one of these amygdalar cell groups (the anterior area) also generates a clear patch of terminal labeling in field CA3. And third, when a qualitative rendering of the total amygdalar input to the HPF is examined, it is immediately apparent that there are three major terminal fields: one is in the ventromedial quadrant of the lateral entorhinal area, adjacent to the lateral edge of the medial entorhinal area; a second is a narrow longitudinal strip overlapping the dorsal half of the border between the medial entorhinal area and the parasubiculum (with inputs to corresponding regions of both cortical fields); and the third is centered in domains 2 and 3 of field CA1/subiculum. In addition, there appear to be two less dense patches or foci of amygdalar inputs to field CA3, one ventral and another more dorsal, adjacent to field CA2 (indicated by arrows in Fig. 7).

It is beyond our scope to list all possible consequences of these amygdalar inputs to the complex circuitry of the HPF. Nevertheless, it is worthwhile pointing out the most obvious influences these pathways may have on information processing within the intrahippocampal circuit, of which the well-known, transversely-oriented trisynaptic circuit [5] forms the skeleton — as well as on the extrinsic projections of the HPF (see Fig. 18 for a schematic version of the HPF flatmap and intrahippocampal circuit).

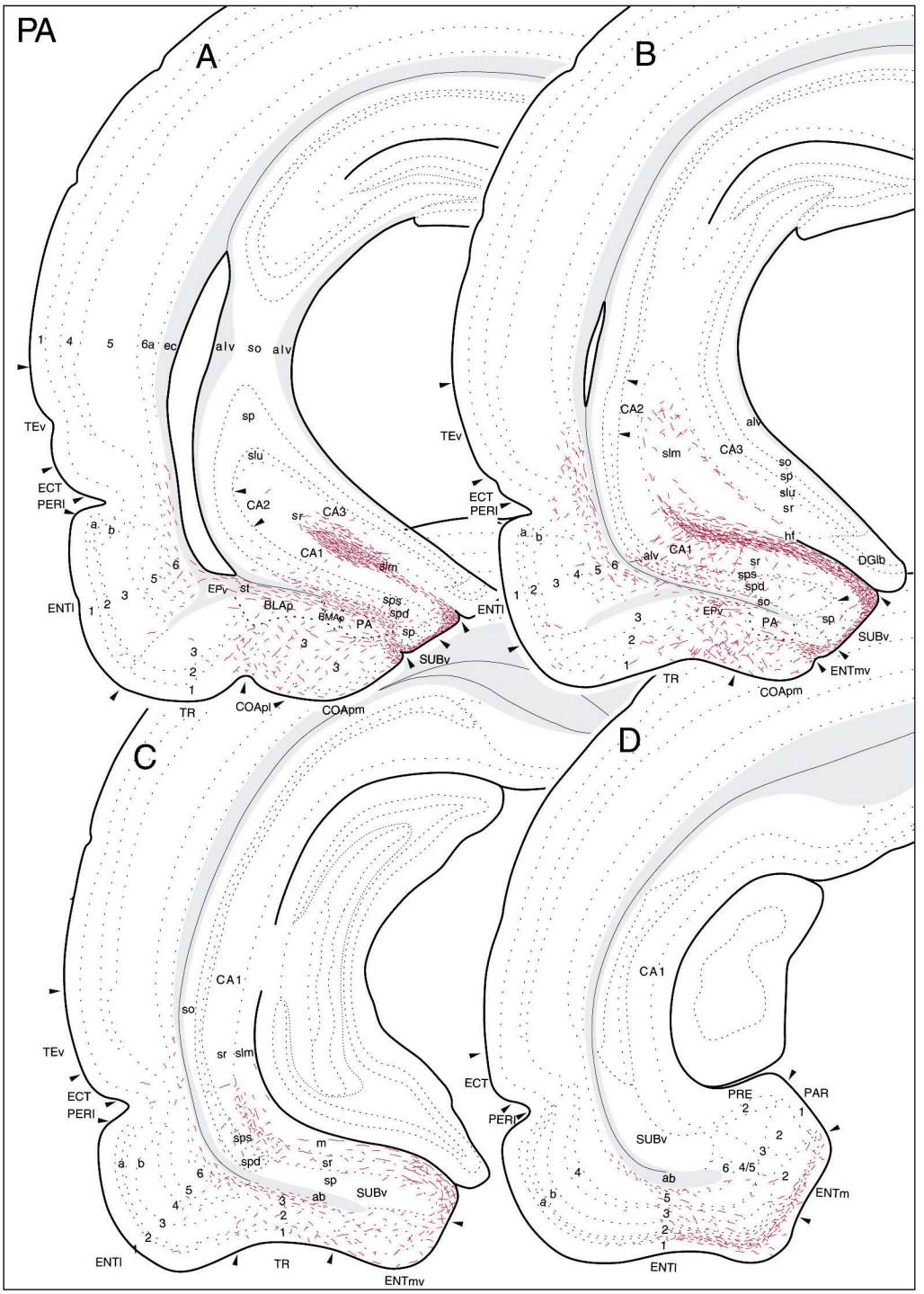


Fig. 17. Distribution of PHAL-labeled projections (red) from the posterior nucleus to the HPF. The results of experiment AHZ18 were plotted onto a series of rat brain atlas templates [134], arranged from rostral (A) to caudal (D).

3.6.1. Amygdalar inputs to intrahippocampal circuitry

Let us start with the entorhinal area, the origin of the perforant path, which in fact innervates all of the other hippocampal cortical areas, but most especially the dentate gyrus [140]. The entorhinal area is very unusual insofar as it innervates virtually all other parts of the cerebral cortical mantle, and a substantial amount of the basal ganglia/cerebral nuclei/striatopallidum as well — but has very little if any input to the diencephalon and lower parts of the brainstem [139]. Entorhinal inputs to the perforant path and other components of the intrahippocampal circuit arise almost exclusively from layers 2 and 3 [68,69,131], and as a whole the amygdala innervates the entire extent of these two layers, in a topographically organized way (Figs. 7

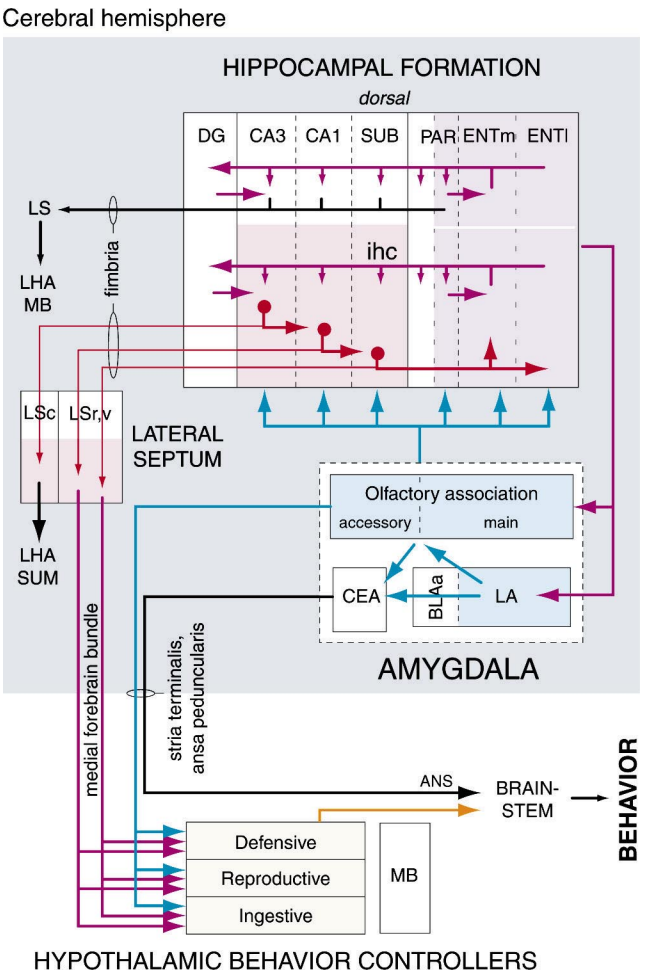


Fig. 18. Schematic overview of projections from the amygdala to the medial hypothalamus, either directly, or via a hippocampo-septal intermediary. Note that amygdalar inputs to the HPF tend to be concentrated in two broad regions: the longitudinal extent of the entorhinal area and parasubiculum (pink), and the ventral half of Ammon's horn and the subiculum (orange). The HPF is shown in a very schematic way, with dorsal or septal at the top and medial or proximal to the left, and with the transversely oriented intrahippocampal circuit (ihc) shown twice (based on Ref. [140]). The actual organization of connections between the amygdala, HPF, septum, and hypothalamus is discussed in the text.

and 8). This means that widespread regions of frontal, insular, and temporal association cortex, as well as gustatory, visceral, olfactory, and accessory olfactory cortical areas have potential access to the perforant path via the amygdala (Fig. 3). An especially dense input to a restricted dorsal part of the medial perforant path arises in the posterior basolateral (parvicellular basal) nucleus, and especially dense inputs to a restricted ventral part of the lateral perforant path arise in the lateral and posterior nuclei and the postpiriform transition area (Figs. 7 and 8).

The amygdalar terminal field in dorsal regions of the medial entorhinal area spills over into layer 2 of the adjacent parasubiculum. This is important because neurons in parasubicular layer 2 project massively to layer 2 of the medial entorhinal area, the origin of the medial perforant path [67,71,150]. A projection to very restricted regions of parasubicular layer 2 appears to arise in the lateral, posterior basomedial, and posterior basolateral nuclei (Figs. 7 and 8), components of the frontotemporal association cortical and main olfactory cortical systems (Fig. 3).

Amygdalar inputs to Ammon's horn and the subiculum have obvious implications for information processing in the transversely organized intrahippocampal circuit: it is well-known that field CA3 projects to field CA1, which massively innervates the subiculum, which in turn projects back to deep layers of the entorhinal area [140]. The two patches or foci of amygdalar inputs to field CA3 imply an influence on Schaffer collateral inputs to two corresponding foci in field CA1 at about the same transverse ('lamellar') levels, just as the massive input to domains 2 and 3 in field CA1 imply a massive influence on a corresponding transverse level in the subiculum, and so on for projections from the subiculum to the entorhinal and other retrohippocampal areas.

In short, various amygdalar cell groups associated with the frontotemporal association cortical, main olfactory, and accessory olfactory systems are in a position to influence very selectively particular transverse levels or 'beams' — or really sets of transverse levels — of the intrahippocampal circuit, and at multiple levels (for example, entorhinal area, field CA1, and field CA3).

It will not be easy to establish the functional dynamics of this complex amygdalo-hippocampal innervation pattern. Nevertheless, a start has been made. For example, electrical stimulation of the lateral nucleus evokes field potentials in the dentate gyrus that are similar to those evoked by perforant path stimulation, but with a longer latency, and lateral nucleus stimulation enhances subsequent dentate responses evoked by perforant path stimulation [147], both effects consonant with an excitatory projection from the lateral nucleus to the entorhinal area [102]. In fact, stimulation of the lateral or basolateral nuclei produces excitation followed by prolonged inhibition in the entorhinal area [24,35]. And finally, whereas stimulation of the medial or posterior basomedial nuclei does not induce LTP in the dentate gyrus, it does increase the magnitude of dentate LTP if applied in conjunction with tetanic perforant path stimulation [51,53], and posterior basomedial or basolateral nucleus lesions attenuate the magnitude of perforant path stimulation-induced LTP in the dentate gyrus [52,54].

3.6.2. Amygdalar inputs to extrinsic HPF projections

Let us now turn to some of the more obvious possible direct amygdalar influences on HPF extrinsic projections. First, because entorhinal layers 4–6 are innervated to some extent by all of the amygdalar cell groups illustrated in Fig. 7, all of them may well influence entorhinal projections to the rest of the cerebral cortical mantle and much of the basal ganglia (cerebral nuclei, striatopallidum) [55,139]. Second, the parasubiculum projects to the mammillary

body, and especially to the lateral nucleus [2,137,138]. However, this projection may arise from neurons just deep to the amygdalar projection to superficial layer 2 [2], and it remains to be determined whether apical dendrites of these slightly deeper parasubiculo-mammillary pyramidal cells are innervated as they pass through the amygdalar terminal field. It is worth noting that the parasubiculum projects to the thalamic anterodorsal nucleus [150] as well as the lateral mammillary nucleus, and that all three of these interconnected cell groups contain head direction neurons [146]. Third, regions of the ventral subiculum innervated by the amygdala give rise to the medial corticohypothalamic tract, which directly innervates the medial hypothalamus [20,63,70,136,137]. This projection will be considered further in Section 4. Fourth, field CA1 and the subiculum project in a topographically ordered way to the rostral and ventral divisions of the lateral septal nucleus, which in turn establishes massive bidirectional connections with particular cell groups in the medial hypothalamus and lower brainstem [112,114]. These projections will be considered further in Section 4. And fifth, field CA3 projects topographically to the caudal division of the lateral septal nucleus, which in turn projects massively to the lateral hypothalamic area and supramammillary nucleus [112,114]. These projections will also be dealt with in Section 4.

Clearly, our structural data support a growing body of evidence indicating functional differentiation along the dorsoventral or longitudinal axis of the hippocampus [94]. A variety of functional evidence suggests that more dorsal regions of the hippocampus play an especially important role in spatial learning, whereas our evidence suggests that ventral regions of field CA1 and the subiculum, in particular, are involved in prioritizing the temporal organization of motivated behavior expression.

3.6.3. Hippocampal projections to amygdala

In closing, at least some mention ought to be made of projections from the HPF to the amygdala. Although they have not been examined systematically, and our knowledge of them may well be very incomplete, it does seem clear that they are substantial and topographically organized, at least in the rat where the most complete information is available. First, the entorhinal area, and its lateral part in particular, sends distinct projections to at least four components of the main olfactory system: the posterior basomedial nucleus [89], posterior basolateral nucleus [89,139,157], cortical nucleus [89], and anterior amygdalar area [89]; as well as to the lateral nucleus [89,139,157], a component of the frontotemporal association cortical system. As shown in Fig. 7, all of these cell groups project to the whole dorsoventral extent of the lateral entorhinal area, except the (posterior) cortical nucleus, which seems to innervate predominantly the ventral half. This is of interest because it would appear that the whole dorsoventral extent of the lateral entorhinal area sends projections back to these same nuclei [89]. Thus, bidirectional connections seem to be established between the lateral entorhinal area and the posterior basomedial, posterior basolateral, posterior cortical, and lateral nuclei, and the anterior amygdalar area. On the other hand, there does appear to be clear topographic order in lateral entorhinal projections to the basolateral complex, and the lateral entorhinal area projects to parts of the amygdala (including the anterior cortical nucleus and nucleus of the lateral olfactory tract) that do not appear to project to it [89]. It is now clear that there are major pathways interconnecting the entire lateral entorhinal area and many components of the amygdala, with the central nucleus being a notable exception.

Second, the ventral subiculum projects massively to the posterior basomedial nucleus; moderately to the posterior nucleus; and lightly to the basolateral, posterior cortical, and medial nuclei, and anterior and postpiriform transition areas [20]. In addition, the topologically medial half of the ventral subiculum (Fig. 19) [100] also projects moderately to the lateral nucleus, especially ventromedially [28,89]. All of these amygdalar cell groups project in a very topographic way on domains 2–5 of the ventral subiculum (Fig. 7). The exact topography of projections between various amygdalar cell groups and domains 2–5 of the ventral subiculum remains to be worked out, but there are hints that the projections may be at least to some extent reciprocal (Fig. 19). In addition, the ventral subiculum appears to project at least moderately to several amygdalar cell groups that do not project back to the HPF, including the nucleus of the lateral olfactory tract and capsular part of the central nucleus [20].

And third, ventral regions only of ammonic field CA1 project at least to the lateral, basolateral, and posterior cortical nuclei [100,149], the posterior nucleus [16,87], the posterior basomedial nucleus [87], and the postpiriform transition area [100]. All of these amygdalar cell groups project topographically to domains 3–5 of the ventral subiculum (Fig. 7), and the precise topography of bidirectional connections between amygdalar cell groups and ventral field CA1 remains to be characterized. However, qualitative comparisons of labeling patterns indicate that at least some of this topography may be quite precise (Figs. 7 and 19). Note that, as with other regions of the HPF, field CA1 does not appear to establish significant connections with the medial and lateral parts of the central amygdalar nucleus.

We are unaware of credible neuroanatomical evidence for a projection from hippocampal field CA3 to the amygdala.

4. Combinatorial amygdalar inputs to hippocampus and hypothalamus

There are at least five major routes for the amygdala to

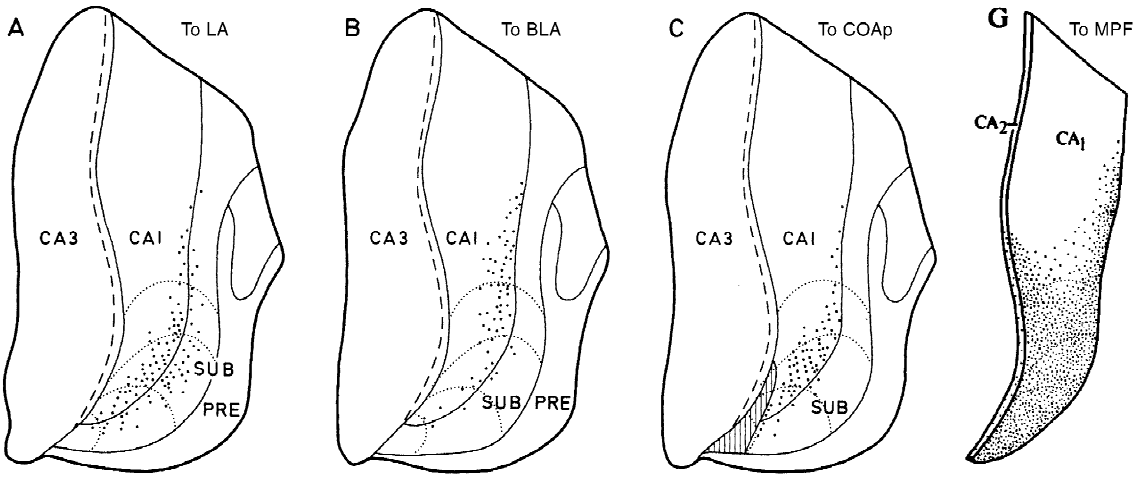


Fig. 19. Distribution of neurons in hippocampal field CA1 and the subiculum (SUB) that project to (and/or through) the lateral (LA, part A), basolateral (BLA, part B), and posterior cortical (COAp, part C) nuclei of the amygdala, and the medial prefrontal cortex (MPF, part G). The neurons were retrogradely labeled with HRP (A–C) or true blue (G) after tracer injection into the indicated cell groups, and their distribution is indicated on the original version of our hippocampal flatmap (Section 3.1). The approximate locations of domains 1–5 (see Fig. 7) have been added to the original figures, which are reproduced with permission from the work of Ottersen (A–C) [100] and Swanson (G) [132].

influence hypothalamic mechanisms (Fig. 20): (1) directly, (2) via hippocampo-hypothalamic projections, (3) via hippocampo-septo-hypothalamic projections, (4) via bed nuclear-hypothalamic projections, and (5) via prefronto-hypothalamic projections. What are the basic organizing principles of these connections from the cerebral hemisphere to the hypothalamus? For the sake of argument, two extreme views are possible. On one hand, different amygdalar cell groups might generate a series of parallel, segregated pathways or circuits to each of the functional subsystems of the hypothalamus, for example, to those controlling ingestive, reproductive, and defensive behaviors (Section 2.1). But on the other hand, individual amygdalar cell groups might project to parts of the HPF and bed nuclei of the stria terminalis that in turn innervate different functional subsystems of the hypothalamus. This scheme involves divergence and convergence of information in targets of amygdalar projections, and is basically a network as opposed to a set of parallel subsystems. Intrinsic to it are mechanisms for extensive interactions between subsystems, and for hypothalamic response prioritization.

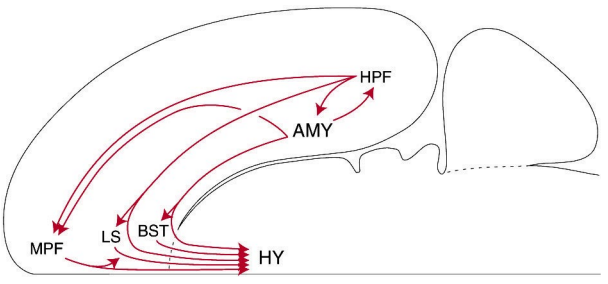


Fig. 20. Summary of five major routes for amygdalar (AMY) information to reach the hypothalamus (HY). As discussed in the text they may be either direct or involve the bed nuclei of the stria terminalis (BST), hippocampal formation (HPF), lateral septal nucleus (LS), or medial prefrontal region of cortex (MPF).

A great deal of research in the cerebral isocortical/dorsal striatopallidal system makes it clear that a combination of neurophysiological and neuroanatomical evidence is required to decide between the two models just outlined [23,57,92]. The goal of this paper is to provide a relatively detailed comparison of structural topography in two sets of amygdalar projections to the hypothalamus — direct and via 'relays' through hippocampo-septal pathways. In the companion paper [33] we review in detail the structural organization of amygdalar projections to the bed nuclei of the stria terminalis. For the sake of completeness, we shall close this section with a brief overview of what is known about the anatomy of direct HPF projections to the hypothalamus, and about projections from the medial prefrontal region to the hypothalamus.

4.1. Comparison of amygdalar inputs to hypothalamus: direct and indirect via HPF

The organization of direct amygdalar projections to the hypothalamus was described in Section 2 and summarized in Fig. 4, whereas the distribution of amygdalar inputs to the HPF was analyzed in Section 3 and summarized in Fig. 7. Our main goal here is to explore how inputs to the HPF from individual amygdalar cell groups may influence the hypothalamus through the intermediary of the lateral septal complex, and to compare this in Fig. 4 with the cell group's direct projection to the hypothalamus. As mentioned in Section 3.6.2, the entorhinal area, which receives extensive inputs from the amygdala, does not project to the hypothalamus, and has little if any input to the lateral septal complex. Furthermore, the only substantial relationship of the parasubiculum, which also receives significant

amygdalar inputs, to the hypothalamus is a direct input to the lateral mammillary nucleus via the descending columns of the fornix. This leaves amygdalar inputs to Ammon's horn and the subiculum to consider.

Current understanding of functional topography in amygdalo-hippocamposepto-hypothalamic circuitry rests on three basic observations. First, progressively more ventral regions of Ammon's horn and the subiculum project to progressively more ventral regions of the lateral septal complex [137], and virtually all pyramidal cells, in Ammon's horn at least, participate in this projection [143]. Second, hippocampal field CA3 preferentially sends axons to the caudal division of the lateral septal nucleus, which is dominated by neurons that express GAD and somatostatin, whereas field CA1 and the subiculum preferentially send axons to rostral as well as ventral divisions of the lateral septal nucleus, which are dominated by neurons expressing GAD/enkephalin and GAD/estrogen receptor, respectively [112–114]. And third, the lateral septal nucleus itself can be divided into on the order of 20 vertically oriented bands of varying dimensions that are defined on the basis of bidirectional connections with specific cell groups in the hypothalamus and lower regions of the brainstem. Furthermore, within the hypothalamus, the caudal division of the lateral septal nucleus (field CA3 input) projects selectively to the lateral zone and supramammillary nucleus, the rostral division (field CA1/subiculum input) projects selectively to the medial nuclei/behavior control column, and the ventral division (ventral tip of field CA1/subiculum input) projects selectively to the periventricular region and neuroendocrine motor zone [112–114].

Based on this evidence, field CA1/subiculum has been divided into a series of five domains, arranged from dorsal to ventral, that project selectively to parts of the lateral septal nucleus that in turn project to specific cell groups of the medial hypothalamus (Fig. 6). As pointed out in Section 3.1, the borders of these recently postulated domains in field CA1/subiculum are still quite provisional, and the domains themselves are not to be regarded as pure populations of neurons influencing a particular hypothalamic nucleus. Instead, each one is probably a focus with progressively diminishing influence dorsally and ventrally. Nevertheless, the structural evidence clearly indicates that different regions of field CA1/subiculum preferentially influence different parts of the rostral and ventral divisions of the lateral septal nucleus, and thus different functional parts of the medial hypothalamus.

The first thing to note about amygdalar inputs to field CA1/subiculum is the relatively small projection to domain 1. The latter corresponds essentially to the dorsal half of field CA1/subiculum, and it is known that the dorsal half of field CA1 projects rather selectively to the tiny dorsal region of the medial zone of the rostral lateral septal nucleus (LSr.m.d.), which in turn projects to the medial septal complex, lateral hypothalamic zone, and supramammillary nucleus [114]. Thus the projections of the zone in the rostral lateral septal nucleus that is projected upon by the field CA1 component of domain 1 are like those of the caudal lateral septal nucleus (with field CA3 input), with which it shares certain chemoarchitectonic features as well (see Fig. 18) [113]. Recall that both the medial septal complex [37] and supramammillary nucleus [43] project massively back to the HPF, and play a critical role in the generation and control of hippocampal theta rhythm [151].

In contrast, the vast majority of amygdalar inputs to field CA1/subiculum are directed toward its ventral half, domains 2–5. Let us begin our comparison of direct and indirect projections with the lateral amygdalar nucleus, which has no direct projection to the hypothalamus (Fig. 4), and not even an input to the bed nuclei of the stria terminalis, which also projects to the hypothalamus. In contrast, because the lateral nucleus projects significantly to domains 2 and 3, it can potentially influence the medial hypothalamic reproductive and defensive behavior controllers via the ventrolateral part of the ventromedial nucleus and anterior nucleus, respectively. This is particularly important in view of the role played by the lateral nucleus in fear conditioning [77]. The anatomical evidence suggests that lateral nucleus projections to the hippocampus (ventral field CA1/subiculum) can in turn influence defensive behavioral responses modulated by the anterior hypothalamic nucleus. The evidence also suggests that this projection modulates influences of feminine sexual behavior on defensive behavioral responses because the ventrolateral part of the ventromedial nucleus is the only part of the reproductive behavior controller known to project substantially to the defensive behavior controller [135].

Thus, whereas the lateral amygdalar nucleus has no direct projection to the hypothalamus, it is in a position to influence coordinated defensive and reproductive behavioral responses via its projection to the HPF, and in particular to ventral field CA1/subiculum. The other amygdalar component of the frontotemporal association cortical system, the anterior basolateral nucleus, appears to have no direct projection to the hypothalamus, and no input to the HPF.

The central nucleus of the amygdala is different: it has little if any projection to the HPF, but instead sends an input directly to restricted regions in the caudal half of the lateral hypothalamic zone (Figs. 4 and 7). These regions (Fig. 5A) contain many preautonomic neurons [121,141] but whether synaptic contacts are established remains to be determined.

Now we come to amygdalar components of the main and accessory olfactory systems, and it is immediately obvious from Fig. 4 that they establish massive direct and indirect (hippocampo-septal) inputs to the hypothalamus, and especially to the behavior control column. Closer examination reveals, however, that the pattern of direct and indirect hypothalamic projections from an individual amygdalar cell group are never identical. As an example

from the main olfactory system, the posterior basomedial nucleus has substantial direct and indirect inputs to the ventrolateral part of the ventromedial nucleus (reproductive behavior controller) and anterior hypothalamic nucleus (defensive behavior controller), but only a direct, and massive, input to the dorsomedial part of the ventromedial nucleus, which we postulate is also a component of the defensive behavior controller. A nice example from the accessory olfactory system would be the posterior amygdalar nucleus. It sends massive direct and indirect projections to all three components of the medial hypothalamic reproductive behavior controller, but only an indirect, though massive, input to the ingestive behavior controller.

The obvious conclusion suggested by our structural analysis is that whereas the amygdala and hippocampus share many bidirectional connections, projections from these regions to the hypothalamus are not arranged in parallel, segregated circuits, at least as far as inputs to nuclei associated with particular classes of motivated behavior are concerned. Instead, there are complex patterns of divergence, and thus convergence as well, in this network of cerebral hemisphere inputs to the hypothalamus. The functional dynamics of this network are essentially unknown, although it appears reasonable to begin with the assumptions that extrinsic projections of HPF pyramidal cells and cortical regions of the amygdala use glutamate as an excitatory neurotransmitter, whereas extrinsic projections of striatal components of the amygdala use GABA as a neurotransmitter [135].

4.2. Other routes for amygdalar influences on hypothalamus

Let us now briefly review other major ways for amygdalar influences to reach the hypothalamus (Fig. 20). We have just discussed the organization of projections from field CA1/subiculum to the lateral septal nucleus and then hypothalamus, so it is convenient to begin here with direct projections from these cortical fields of the HPF to the hypothalamus. In the first place, all dorsoventral levels of the subiculum project to the medial mammillary nucleus via the descending column of the fornix, although the density of neurons participating in this projection may decrease progressively along the ventral dimension [63,97,136,137,156]. In contrast, ventral regions of the subiculum (and perhaps to a limited extent immediately adjacent regions of field CA1) innervate parts of the medial hypothalamus rostral to the mammillary body via the medial corticohypothalamic tract [20,63,70,96,97,136,137], which splits off from the fornix just caudal to the anterior commissure.

From the structural data available to date it is clear that the medial corticohypothalamic tract is topographically organized, although precise details remain to be worked out because there are dorsoventral as well as mediolateral gradients at play (see Fig. 7 and Ref. [96]). Nevertheless, it would appear from PHAL experiments that subicular domains 2–4 project substantially to the anterior hypothalamic nucleus, with most of the projection coming from domains 2 and 3 (Ref. [63], their Figs. 3, 5, 8, and 10); and that there is only a light projection to the medial preoptic nucleus, from domains 2–4 (Ref. [63], their Figs. 3, 5, and 8). In addition, PHAL injections in domain 3 and adjacent regions of domain 4 label substantial inputs to the ventrolateral part of the ventromedial nucleus and ventral premammillary nucleus [20]. Precisely in what manner direct subiculohypothalamic and indirect subiculo-septo-hypothalamic projections map onto one another remains to be determined, but it seems obvious that there is at least some overlap. Perhaps the situation is like that described for direct and indirect inputs to the medial hypothalamus from olfactory-related amygdalar nuclei (Section 4.1 and Fig. 4).

Interestingly, the part of field CA1 that receives inputs from the amygdala also projects to the medial prefrontal cortex, to a contiguous region that includes the infralimbic, prelimbic, and medial orbital areas (see Fig. 19G and Refs. [56,132,149]). Also, more or less the entire dorsoventral extent of the subiculum innervates this same prefrontal region [56,96,137,156], although projecting neurons are apparently restricted to the medial or proximal half of the subiculum, and here they are most concentrated in the intermediate third along the longitudinal axis [56]. One reason this is so interesting is that the region of field CA1/subiculum that projects to the orbitofrontal cortex is strikingly reminiscent of the region that receives input from the amygdala, except for the dorsal end of the subiculum (Fig. 7).

This is also interesting because at least one part of the hippocampal recipient zone of the orbitofrontal region, the infralimbic area, projects massively upon two parts of the medial hypothalamic behavior control column — the medial preoptic and anterior hypothalamic nuclei (Fig. 21). Recall that they are parts of the reproductive and defensive behavior controllers, respectively (Fig. 4), and that both receive inputs from the medial corticohypothalamic tract, which arises in approximately same region of field CA1/subiculum that projects to the orbitofrontal region (Section 4.1). In addition, the adjacent prelimbic area heavily innervates the dorsal premammillary nucleus [25], a key component of the defensive behavior controller (Section 2.1), and also projects to as yet ill-defined regions of the lateral zone [9,22,126].

5. Overview

Since the introduction of axonal transport pathway tracing methods in the early 1970s there has been a stunning, overwhelming increase in our knowledge of amygdalar connections. This is easy to verify by reviewing the critical experimental degeneration analysis of rat

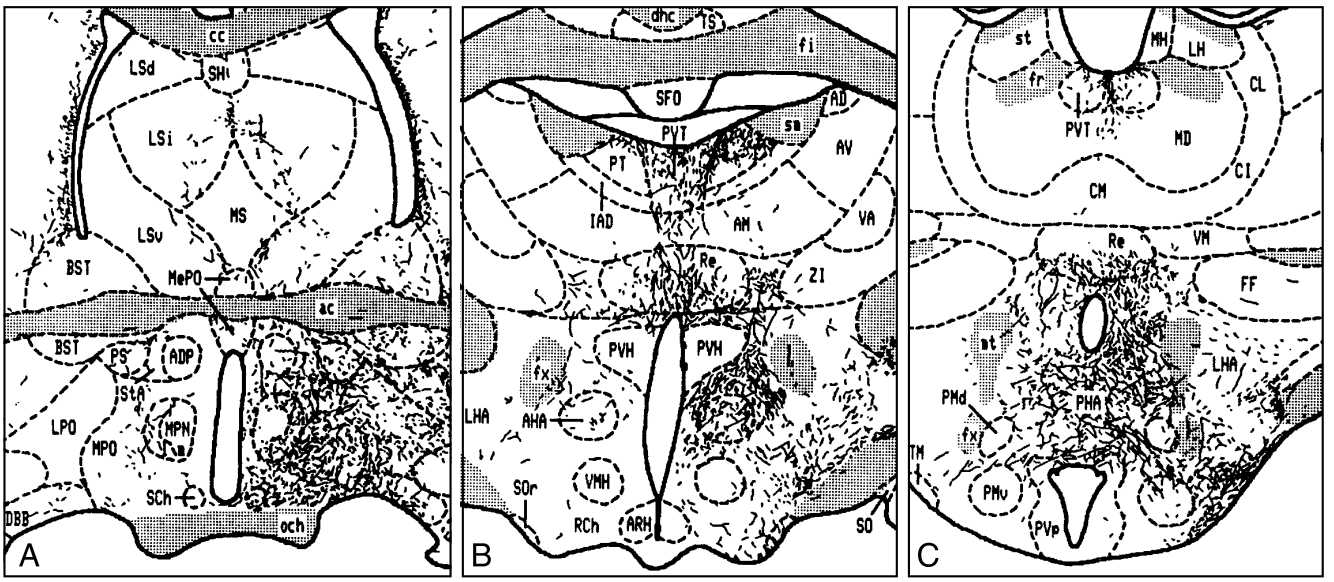


Fig. 21. Distribution of inputs from the infralimbic area of the prefrontal cortex to selected levels of the hypothalamus. Although there are several good accounts of overall projections from the infralimbic area [50,145], the most detailed description of hypothalamic terminal fields comes from the PHAL analysis of Brittain [12], where every labeled axon in the histological sections was plotted with the aid of a computer graphics system and motorized stage. Drawings of transverse sections arranged from rostral (A) to caudal (C). Reproduced with permission from Ref. [12].

amygdalar connections published by Cowan, Raisman, and Powell in 1965 [26]. The full extent of their conclusions may be stated accurately in a few sentences, partly because connections of individual cell groups were not known. First, unambiguous amygdalar projections were restricted to the stria terminalis and were traced to three terminal fields — the bed nuclei of the stria terminalis, nucleus accumbens, and rostral hypothalamus (including the medial preoptic and anterior hypothalamic areas) — and they appeared to arise from both the corticomedial and basolateral groups of amygdalar nuclei. And second, unambiguous inputs to the amygdala were identified from the olfactory bulb (to the corticomedial group), piriform cortex (to the basolateral group), and rostral hypothalamus (to both groups, via both the stria terminalis and ventral pathway). No inputs to the central nucleus could be identified.

Today, on the order of 20 amygdalar cell groups (some of which are distinct subdivisions of major cell groups like the central, medial, or lateral nuclei) are generally recognized, and the connections of most of them have been analyzed with sensitive axonal transport tracer methods. It would appear that, on average, each cell group projects to about 15 sites, and receives inputs from about the same number of distinct brain regions. Thus, on the order of 600 or so amygdalar connections are now known, and it would not be surprising if a thousand or so were not eventually identified. This incredibly rich set of structural data, which is supplemented with neurotransmission information about many of the connections, provides the opportunity for a completely fresh perspective on the place of amygdalar cell groups in the scheme of cerebral circuitry. Nothing approaching a rigorous synthesis has been attempted, but our own overview [142] suggests at least that the amygdala is neither a structural nor a functional entity. Instead, we suggested that it might be helpful to view its various cell groups as components of at least four broad cortico-striatopallidal systems — accessory olfactory, main olfactory, autonomic, and frontotemporal association (Fig. 3) — which themselves may share certain interconnections, just like other differentiated parts of the cortico-striatopallidal system [135].

The sorting of amygdalar cell groups into components of accessory olfactory, main olfactory, autonomic, and frontotemporal association systems may prove to be inaccurate or incomplete, but it does at least help attempts to clarify the organizing principles of connections between the amygdala, hippocampus, septum, and hypothalamus (Figs. 4 and 18). Needless to say, dramatic increases in structural knowledge have not been confined to the amygdala. Over 20 clear divisions of the lateral septal nucleus have recently been analyzed [113,114], there are the same order of parts in the bed nuclei of the stria terminalis [59,60], and the hypothalamus probably has at least 50 to 100 differentiable cell groups. In the face of all this evidence, it is surprising indeed that most current thinking about amygdalar and hippocampal function ignores their massive, highly organized descending input to the hypothalamus.

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