

Interactive review

Topography of projections from amygdala to bed nuclei of the stria terminalis[☆]

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Abstract

A collection of 125 PHAL experiments in the rat has been analyzed to characterize the organization of projections from each amygdalar cell group (except the nucleus of the lateral olfactory tract) to the bed nuclei of the stria terminalis, which surround the crossing of the anterior commissure. The results suggest three organizing principles of these connections. First, the central nucleus, and certain other

Abbreviations: AAA: anterior amygdalar area; ACAd1–6: anterior cingulate area, dorsal part, layers 1–6; ACB: nucleus accumbens; ac: anterior commissure; aco: anterior commissure, olfactory limb; act: anterior commissure, temporal limb; ADP: anterodorsal preoptic nucleus; AHA: anterior hypothalamic area; AHNc: anterior hypothalamic nucleus, central part; alv: alveus; amc: amygdalar capsule; apd: ansa peduncularis; b.: basal nucleus amygdala [Johnston]; b. acc.: accessory basal nucleus amygdala [Johnston]; BLAa,p: basolateral nucleus, anterior, posterior parts; BMAa,p: basomedial nucleus, anterior, posterior parts; BST: bed nuclei of the stria terminalis; BSTa: bed nuclei of the stria terminalis, anterior division; BSTad(c,r): bed nuclei of the stria terminalis, anterior division, anterodorsal area (caudal, rostral regions); BSTal(c,r): bed nuclei of the stria terminalis, anterior division, anterolateral area (caudal, rostral regions); BSTam: bed nuclei stria terminalis, anterior division, medial group; BSTav: bed nuclei of the stria terminalis, anterior division, anteroventral area; BSTcc: bed nuclei of the stria terminalis, anterior division, anterodorsal area, central core; BSTd: bed nuclei of the stria terminalis, posterior division, dorsal nucleus; BSTdl: bed nuclei of the stria terminalis, anterior division, dorsolateral nucleus; BSTdm: bed nuclei of the stria terminalis, anterior division, dorsomedial nucleus; BSTfu: bed nuclei of the stria terminalis, anterior division, fusiform nucleus; BSTif: bed nuclei of the stria terminalis, posterior division, interfascicular nucleus; BSTju: bed nuclei of the stria terminalis, anterior division, juxtacapsular nucleus; BSTmg: bed nuclei of the stria terminalis, anterior division, magnocellular nucleus; BSTov: bed nuclei of the stria terminalis, anterior division, oval nucleus; BSTp: bed nuclei of the stria terminalis, posterior division; BSTpr: bed nuclei of the stria terminalis, posterior division, principal nucleus; BSTrh: bed nuclei of the stria terminalis, anterior division, rhomboid nucleus; BSTsc: bed nuclei of the stria terminalis, anterior division, subcommissural zone; BSTse: bed nuclei of the stria terminalis, posterior division, stria extension; BSTsz: bed nuclei of the stria terminalis, posterior division, cell sparse zone; BSTtr: bed nuclei of the stria terminalis, posterior division, transverse nucleus; BSTv: bed nuclei of the stria terminalis, anterior division, ventral nucleus c.a., anterior commissure; CA1–3: hippocampal/ammic fields CA1–3; CEAc,l,m: central amygdalar nucleus, capsular, lateral, medial parts; c.i.: internal capsule; CLA: claustrum; COAa,pl,pm: cortical nucleus amygdala, anterior, posterolateral, posteromedial parts; com: stria terminalis, commissural part; cort.: cortical nucleus amygdala; CP: caudoputamen; cpd: cerebral peduncle; d.b.: diagonal band; ec: external capsule; ENT11–6: lateral entorhinal area, layers 1–6; ENTmv: entorhinal area, medial part, ventral zone; EPd,v: endopiriform nucleus, dorsal, ventral parts; fa: corpus callosum, anterior forceps; fx: columns of the fornix; GABA: gamma-amino butyric acid; GLU: glutamate; GPe,i: globus pallidus, external, internal parts; h.: hippocampal formation; HY: hypothalamus; IA: intercalated nuclei amygdala; IG: induseum griseum; ILA: infralimbic area; int: internal capsule; LA: lateral amygdalar nucleus; l.b.: longitudinal association bundle; LHA: lateral hypothalamic area; lot: lateral olfactory tract; LPO: lateral preoptic area; l. pyr.: pyriform lobe; LSr: lateral septal nucleus, rostral part; LSv: lateral septal nucleus, ventral part; m.: medial nucleus amygdala; MEAad,pd,pv: medial amygdalar nucleus, anterodorsal, posterodorsal, posteroventral parts; MPN: medial preoptic nucleus; MPO: medial preoptic area; MS: medial septal nucleus; NDB: nucleus of the diagonal band; NLOT1–3: nucleus of the lateral olfactory tract, layers 1–3; n.o.a.: anterior olfactory nucleus; n.t.o.l.: nucleus of the lateral olfactory tract; nuc. am. c.: central nucleus amygdala; nuc. am. l.: lateral nucleus amygdala; opt: optic tract; OT: olfactory tubercle; PA: posterior amygdalar nucleus; PAA1–3: piriform-amygdalar area, layers 1–3; PERI: perirhinal area; PIR1–3: piriform area, layers 1–3; PL1–6: prelimbic area, layers 1–6; pre: stria terminalis, precommissural part; post: stria terminalis, postcommissural part; PS: parastria nucleus; PVH: paraventricular nucleus hypothalamus; REa: nucleus reuniens, rostral division, anterior part; SF: septofimbrial nucleus; SH: septohippocampal nucleus; SIc,r: substantia innominata, caudal, rostral regions; sm: stria medullaris; SO: supraoptic nucleus; st: stria terminalis; STN: subthalamic nucleus; SUBv: ventral subiculum; THAL: dorsal thalamus; t.o.: olfactory tubercle; TR: postpiriform transition area; TRS: triangular nucleus septum; TTD1–4: tenia tecta, dorsal part, layers 1–4; TU: tuberal nucleus hypothalamus; VL: lateral ventricle; VMH: ventromedial nucleus hypothalamus; ZI: zona incerta

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amygdalar cell groups associated with the main olfactory system, innervate preferentially various parts of the lateral and medial halves of the bed nuclear anterior division, and these projections travel via both the stria terminalis and ansa peduncularis (ventral pathway). Second, in contrast, the medial nucleus, and the rest of the amygdalar cell groups associated with the accessory and main olfactory systems innervate preferentially the posterior division, and the medial half of the anterior division, of the bed nuclei. And third, the lateral and anterior basolateral nuclei of the amygdala (associated with the frontotemporal association cortical system) do not project significantly to the bed nuclei. For comparison, inputs to the bed nuclei from the ventral subiculum, infralimbic area, and endopiriform nucleus are also described. The functional significance of these projections is discussed with reference to what is known about the output of the bed nuclei.

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1. Introduction

The cerebral hemisphere gray matter that surrounds the stria terminalis — from the temporal pole caudally to the base of the olfactory peduncle rostrally — was defined originally by J.B. Johnston in 1923 as the bed of the stria

terminalis [45]. The temporal end of Johnston's bed of the stria terminalis is now regarded as the main part of the amygdala, and only a few neurons can be traced along the body of the stria terminalis, in the rat at least [54,90]. In contrast, the rostral end of Johnston's bed of the stria terminalis, which lies just ventral to the lateral septal

nucleus and just dorsal to the preoptic region of the hypothalamus, surrounding the crossing of the anterior commissure, has come to be referred to as the bed nuclei (or bed nucleus) of the stria terminalis (BST) in mammals.

A vast physiological literature indicates that the amygdala can influence profoundly a variety of visceromotor responses as well as the expression of instinctive and conditioned behaviors with a motivational and/or emotional component (for reviews see [1,23,33,50,53,60,78,107]). In a companion paper [74] we have reviewed how these influences could be mediated by projections from the amygdala directly to the hypothalamus and lower brainstem, as well as by projections from the amygdala to other parts of the cerebral cortex including the hippocampus and medial prefrontal region — which in turn project directly or indirectly via the basal ganglia/cerebral nuclei/striatopallidal system to the hypothalamus and lower brainstem. Here we consider in detail the organization of yet another potential route, via the BST, which are known to project massively to the hypothalamus and lower brainstem [29–31,42,105].

It was known in a general way from normal [45] and experimental degeneration (e.g., [20,25,28,40,54]) material that the amygdala provides a major input to the BST. However, it was the pioneering autoradiographic analysis of Krettek and Price [51] that showed how individual cell groups associated with the amygdala project in a topographically ordered way upon the BST, which they parcelled into basic medial and lateral divisions. They concluded that the lateral division of the BST is innervated by the central and basolateral nuclei of the amygdala, that the medial division of the BST is innervated by the medial and posterior cortical nuclei and the amygdalo–hippocampal area (posterior nucleus), and that a central zone of the BST (which includes parts of both the medial and lateral divisions) is innervated by the basomedial nucleus. Several years later Weller and Smith arrived at similar conclusions based on the HRP retrograde tracer method [115].

In the two decades following this seminal work a great deal has been learned about the structural, and presumably functional, organization of the BST. From our own perspective, the most important advance was the basic division in 1989 of the BST into anterior and posterior (rather than medial and lateral) components and the recognition of some 20 distinct cell groups within them, based on a combination of cyto- and chemoarchitectonic criteria [47,48]. Since then, accumulating evidence indicates that at least some of the cell groups we recognized are innervated by different amygdalar cell groups [12,14,18,73,75,76,97], and generate distinct projection patterns [29–31,63,80,95]. Presumably, an even more fine-grained analysis of connections associated with individual BST cell groups will help clarify functions ascribed to the BST as a whole, including neuroendocrine and autonomic responses [22,36,55,98,99], stress responses (e.g., [16,24,32,41]), responses to withdrawal from drugs of

abuse [6], salt appetite [44], and the expression of social behaviors [80].

Since the last comprehensive examination of amygdala to BST projections [51], the PHAL method for anterograde tracing has been established. It has three main advantages over the autoradiographic method. First, it is more sensitive; second, even more circumscribed, easy to delineate injection sites can be produced; and third and of primary importance, the morphology of labeled axons is observed with the clarity of Golgi impregnations; sometimes ambiguous patterns of silver grains need not be interpreted. The data presented here is fundamentally important for interpreting the results of our ongoing analysis of projections from each of the cell groups currently recognized in the BST.

2. Materials and methods

A total of 125 PHAL experiments, each with an injection site involving one part of the amygdala or another, were available for this analysis. The overall projection pattern labeled in many of these experiments has already been described in detail [12,14,73,75,76], along with exactly how the histological material was produced. Additional experiments with injections in other parts of the amygdala were also available, as indicated below, and were prepared in the same way, as were experiments used to describe the output of the ventral subiculum [15] and infralimbic area [11]. Briefly, each animal received a single iontophoretic injection of a 2.5% solution of PHAL through a stereotaxically positioned glass micropipette (tip diameter 10–15 μm) by applying a +5–8 μA current, pulsed at 7 s intervals, for 10–20 min. Postinjection survival times ranged between 14 and 18 days, and the perfusion-fixed frozen brains were cut at 30 μm on a sliding microtome. One complete series of sections (typically 1-in-4) was processed for immunohistochemistry with an antiserum directed against PHAL (Dako Laboratories) at a dilution of 1:1000 and the antigen–antibody complex was localized by using a variation of the avidin–biotin complex system (ABC Elite Kit, Vector Laboratories). An adjacent series was always stained with thionin to serve as a reference series for cytoarchitectonic purposes. Sections were examined with a Leitz Laborlux D microscope using both bright- and darkfield illumination.

For all relevant experiments a rather complete description of inputs to the BST has been provided graphically on a standard series of eight templates from transverse sections of the adult male Sprague–Dawley rat using procedures described fully elsewhere [100]. For experiments already published, additional levels through the BST were added to complete the eight section set. Parcellation of the brain, and the terminology used for describing

morphological features of PHAL-labeled axons, follows Ref. [100].

3. Overview of amygdalar and BST structural organization

There is still some disagreement about the exact parceling and nomenclature of the mammalian amygdalar region in the literature, which is reviewed in the companion paper [74]. The current version of our own structural model [74,101,107] views amygdalar cell groups as components of four cortico-striatopallidal functional systems: accessory olfactory, main olfactory, autonomic, and frontotemporal association (Fig. 1).

As mentioned in Section 1, Krettek and Price [51,52] used a basic medial/lateral division of the BST, which had been introduced earlier by Bleier [10], and much more refined versions of this approach have since been published (e.g., [2,26,63]). In contrast, Bayer [7] identified a basic anterior/posterior division of the rat BST on developmental grounds, and we [47,48] elaborated upon this view independently using cyto- and chemoarchitectonic criteria in the adult. As shown below, these ways of viewing the organization of amygdalar and BST cell groups help greatly in understanding the organization of presently known connections between them. A comparison of what are now the most frequently used parcellations of the rat BST is provided in Fig. 2, and more detailed analyses of this problem may be found in Refs. [2,27,48,63]. Our current parcellation has only one minor variation on the scheme proposed originally [47,48]. Because of their similar inputs from the amygdala (Fig. 3) the fusiform nucleus and adjacent subcommissural zone are grouped with the anterolateral rather than the anteroventral area of the anterior division.

The anterior division of the BST has been separated into anterodorsal, anterolateral, and anteroventral areas with somewhat vaguely defined borders, and embedded within these three areas various relatively obvious cell groups or nuclei have been identified (see Fig. 6). Specifically, juxtacapsular, oval, rhomboid, and fusiform nuclei are found in the anterolateral area, along with a subcommissural zone; and dorsomedial, dorsolateral, magnocellular, and ventral nuclei are found in the anteroventral area. Based on the present results, and on the emerging results of our PHAL analysis of BST projections [29–31], the cell groups of the anterior division have been arranged provisionally into medial and lateral groups. The medial group of the anterior division is characterized by, though certainly not limited to, dense projections to regions of the hypothalamus closely associated with the neuroendocrine system, and includes the anterodorsal and anteroventral areas. In contrast, the lateral group of the anterior division is characterized by, though again not limited to, projections to autonomic-related parts of the hypothalamus and lower

brainstem, and includes the anterolateral area and its four clear differentiations (the juxtacapsular, oval, rhomboid, and fusiform nuclei).

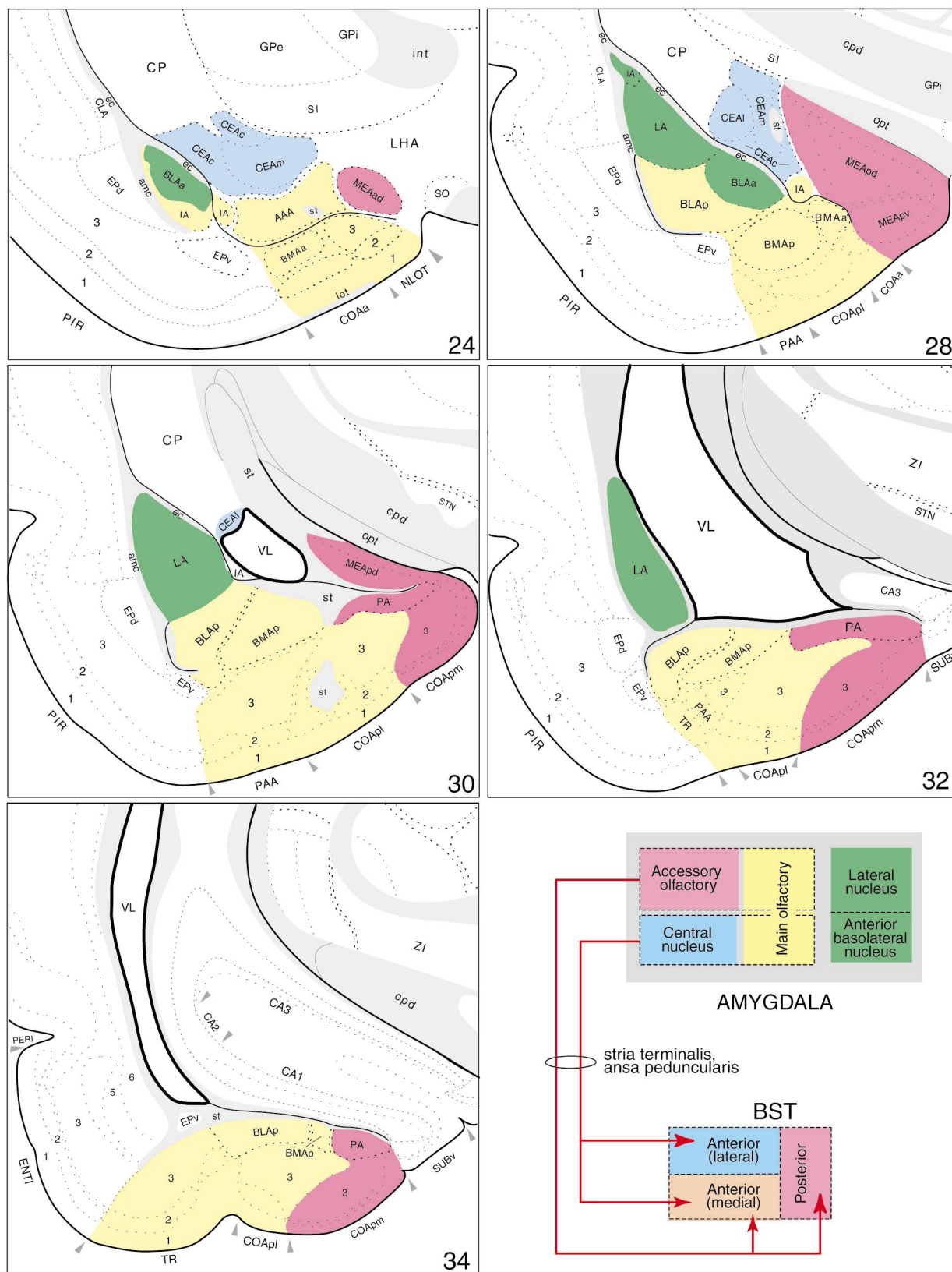
The posterior BST division has at least five distinguishable regions: the dorsal, principal, interfascicular, and transverse nuclei, and the cell-sparse zone. This division is characterized by inputs from the medial nucleus of the amygdala and projections to the medial nuclei of the hypothalamus [13,14,93–95].

4. Projections from amygdala to BST

Before exploring the details of this massive projection system it is useful to consider an overview of the results (Fig. 1). To begin with, axons from the amygdala reach the BST via two distinct pathways, the stria terminalis (dorsal pathway) and the ansa peduncularis (ventral pathway). Amygdalar cell groups associated with various functional systems innervate distinctive regions of the BST via the stria terminalis and/or ansa peduncularis. The central nucleus, which can be thought of as a caudal differentiation of the striatum specialized for autonomic responses, innervates predominantly the anterior division, and within it targets more densely the lateral group. In contrast, the medial nucleus, which can be thought of as another caudal differentiation of the striatum specialized instead for pheromone-induced responses, innervates preferentially the posterior division of the BST. However, the medial nucleus and other amygdalar components of the pheromonal system (the posterior and posteromedial cortical nuclei) also innervate the medial group of the anterior division. Amygdalar components of the main olfactory system seem to fall into two groups on the basis of their inputs to the BST. One group shares with the central nucleus dense inputs to the lateral group of the anterior division; included here are the anterior amygdalar, anterior cortical, and postpiriform transition areas, and the anterior basomedial and posterior basolateral nuclei. The other group shares with the accessory olfactory system dense inputs to the posterior division of the BST and/or to the medial hypothalamus; included here are the piriform-amygdalar and posterolateral cortical areas and the posterior basomedial nucleus. Finally, amygdalar cell groups associated with the frontotemporal system (the lateral and anterior basolateral nuclei) provide virtually no direct input to the BST.

4.1. Projections from the autonomic system

Projections to the BST from each of the three major recognized parts (medial, lateral, and capsular) of the central amygdalar nucleus will be described. The results of these experiments, and the rest of those described in Sections 4 and 5 are summarized in Fig. 3.



Ju & Swanson, 1989 [xx]; Ju et al., 1989 [xx]; Swanson, 1992 [xx]; Swanson, 1998 [xx]				de Olmos et al. 1985 [xx]		Alheid et al. 1995 [xx]		Paxinos & Watson		Moga et al. 1989 [xx]		
								1986 [xx]	1998 [xx]			
Anterior division	Medial group	Anterodorsal area	ad (r) & cc	MA (medial division, anterior)	MA	MA (medial division, anterior)	MA	AM (anterior medial)	Medial division			
			ad (c)									
		Anteroventral area	av	V (ventral division)	MV (medial division, ventral)	V (lateral division, ventral)	MV (medial division, ventral)	VM (ventral medial)				
			dm									
			mg	I (intermediate division), MPIgc (medial division, posterior part, large-celled column) ?	LI (lateral division, intermediate), MPI (medial division, posterior part, lateral column)?	I (intermediate division), MPI, MPL (medial division, posterointermediate, posterolateral)	MPI, MPL ?	PO (preoptic)				
			dl									
			v									
	Lateral group	Anterolateral area	al(r)			L (lateral division)	L		Lateral division			
			ju	LJ (lateral division, juxtacapsular)	LJ	LJ (lateral division, juxtacapsular)	LJ	JXC (juxtacapsular)				
			ov	LD (lateral division, dorsal)	LDC & LDCn (capsular & central parts of LD)	LD (lateral division, dorsal)	LD	DL (dorsal lateral)				
			fu			Fu?	Fu (fusiform part)	VL (ventral lateral)				
			rh	I (intermediate division)	LI (lateral division, intermediate)	LD?, I (intermediate division)	LP (lateral division, posterior)	PL (posterior lateral)				
			sc	LV (lateral division, ventral)	LV	LV (lateral division, ventral)	LV	AL (anterior lateral), PL (posterior lateral)				
			al(c)	LP (lateral division, posterior), I	LP, LI	I, LP (lateral division, posterior)	LP, LI (lateral division, intermediate)					
Posterior division		tr	MPmec (medial division, posterior part, medium-celled column)	MPI (medial division, posterior part, intermediate column), MPI	MPI, MPL	MPL	PI (posterior intermediate), PO (preoptic)	Medial division				
	if	MPIgc (medial division, posterior part, large-celled column)	MPI (medial division, posterior part, lateral column)									
	pr	MPsc (medial division, posterior part, small-celled column), MPmec	MPm (medial division, posterior part, medial column), MPI	MPM (medial division, posteromedial), MPI	MPM, MPI	PM (posterior medial), PI						
	d					SV (subventricular), PI						
	se	S (supracapsular)	S (supracapsular)	S (supracapsular)	S (supracapsular)	SC (supracapsular)						

Fig. 2. Comparison of our BST parcellation with other current schemes. The early work of Bleier [10] and Krettek and Price [51] simply used medial and lateral divisions. In 1985 de Olmos et al. [26] introduced the first detailed parcelling, based on medial, lateral, intermediate, and ventral divisions. A decade later they [2] returned to medial and lateral divisions, which Moga et al. [63] parcellled in an alternative way. As can be seen, the Paxinos and Watson atlas editions of 1986 and 1998 [71,72] have, with a few modifications, followed the de Olmos schemes. In contrast, our model is based on anterior and posterior divisions, a view supported by the embryological work of Bayer [7]. As can be seen in this Figure, the medial–lateral and anterior–posterior schemes are compatible. The medial group of the anterior division and the posterior division are comparable to the medial division, whereas the lateral group of the anterior division is comparable to the lateral division.

4.1.1. From the medial part of the central nucleus

The description of projections from this cell group is based mainly on experiment CEAm#2. As shown in Figs. 4 and 5, the PHAL injection site is confined almost entirely to the medial central nucleus, although a very few labeled neurons were observed in immediately adjacent regions of the substantia innominata.

PHAL-labeled axons extend from the injection site through both the stria terminalis and ansa peduncularis to converge upon the BST. As shown in Figs. 3 and 6, the medial central nucleus generates very dense terminal fields in the lateral group of the anterior division, including the anterolateral area and its oval, fusiform, and rhomboid nuclei, and its subcommissural zone (Fig. 6C–F). Of these,

Fig. 1. Overview of amygdalar and BST structural relationships in the rat. It is convenient to associate amygdalar cell groups with four corticostriatal functional systems, as indicated in this series of five drawings from transverse sections through the left temporal region of the cerebral hemisphere (atlas levels [100] indicated in lower right of each box, arranged from rostral, 24, to caudal, 34). As shown in the lower right diagram, and explained in the text, pink amygdalar structures are most closely associated with the accessory olfactory system, yellow with the main olfactory system, blue with the autonomic system, and green with the frontotemporal association system. Projections from the amygdala course through the stria terminalis and ansa peduncularis to reach the BST, where axons from both routes seem to intermingle extensively. The present analysis indicates that the central amygdalar nucleus (autonomic system) and parts of the main olfactory system innervate almost exclusively the anterior BST division, whereas the accessory olfactory system and other parts of the main olfactory system innervate the posterior BST division along with the medial group of the anterior division. Frontotemporal system components (lateral and anterior basolateral nuclei) apparently do not project directly to the BST at all.

TO BED NUCLEI OF THE STRIA TERMINALIS																													
<div>To</div> <div>From</div>				FROM AMYGDALA																				OTHER					
				Frontotemporal system		Autonomic system				Main olfactory system								Accessory olfactory system											
				LA	BLAa	CEAl	CEAm	CEAc(v)	CEAc(l)	AAA	BMAa	COAa	BLAp	TRr	TRcm	TRcl	BMAp	PAA	COApI	COApm	MEAad	MEApv	MEApd	PA	SUBv	ILA	EPv		
Anterior division	Medial group	Anterodorsal area	ad(r) & ad(cc)	–	–	+	++	+++	–	++	++++	+	++	++++	+++	+	++	+	++	++	++	+++	++	+	++	+++	–	+	
			ad(c)	–	–	–	–	+	–	+	++	++	+	–	+++	+	–	+++	+++	+++	+++	+++	+++	+++	+++	+++	+	+	
		Anteroventral area	av	–	–	–	++	+++	+	++	++++	–	++	+++ (r)	fp	–	+	–	++	–	++	–	++	+	–	–	+	++	+
			dm	–	–	–	+	++	–	++	++++	–	++	+++	+	–	++	+	++	+	+++	+	–	–	–	–	+	+++	+
			mg	–	–	–	+	++	–	–	+	–	+	fp	–	–	+++	–	+	–	+++	+,fp	++	+	–	–	+	++	+
			dl	–	–	–	–	fp	–	–	++	–	fp	fp	–	–	–	–	+	–	+++	++	+	–	–	fp	+	–	
			v	–	–	–	–	+	–	fp	+++	–	fp	fp	–	–	–	–	++	–	+++	fp	–	–	–	–	fp	++	–
	Lateral group	Anterolateral area	al(r)	–	–	–	–	+	–	+	+	–	+++	++++	–	–	++	+	–	–	–	–	–	–	–	–	fp	++	+
			ju	–	–	–	–	–	–	–	–	–	–	+++	++++	–	+++	–	–	–	–	–	–	–	–	–	–	–	–
			ov	–	–	+++	+++	+	–	–	++	–	–	++++	–	+++	–	–	–	–	–	–	–	–	–	–	–	–	–
			fu	–	–	+++	+++	+++	+	–	+	–	–	+	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
			rh	–	–	+	++++	+++	+	+++	++++	–	+++	+++	–	fp	–	–	–	–	–	fp	–	–	–	–	–	–	–
			sc	–	–	+	+++	++++	++	+++	++++	–	+++	++++	–	–	+	–	–	–	–	+	–	–	–	–	fp	–	–
			al(c)	–	–	+++	+++	++++	+++	+++	++++	–	+++	++++	fp	–	+	–	+	–	–	–	++	–	–	–	–	fp	–
Posterior division			tr	–	–	fp	++	+	fp	++(l)	+++ (l)	+	+	fp	fp	fp	+	+++	+++	+++	+++	++++	++++	fp	fp	+++	+	+	
			if	–	–	–	fp	–	–	fp	fp	+	fp	fp	–	–	–	+++	+++	+++	+++	++++	++++	fp	fp	+++	+	+	
			pr	–	–	–	–	–	–	–	–	+(r)	–	–	–	–	–	–	–	+	++	++	++++	++++	–	–	–	–	
			d	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	++	–	–	–	+	+++	++	–	–		

Fig. 3. Summary of anatomically defined projections from amygdala and several other cerebral regions (columns) to BST (rows) in adult male rat. Crosses indicate relative strength of connections in qualitative terms: + + + +, very dense; + + +, dense; + +, moderate; +, light; –, none observed. Abbreviations for amygdalar and BST cell groups are in the abbreviation list. Other abbreviations: cl, caudolateral; cm, caudomedial; fp, fibers-of-passage; l, lateral; r, rostral; v, ventral.



Fig. 4. PHAL injection sites involving various different regions of the central amygdalar nucleus. Each immuno-labeled neuronal cell body in a series of transverse, 30 μm -thick frozen sections through the rostrocaudal extent of the injection site was plotted with the aid of a camera lucida, and cytoarchitectonic boundaries were determined using adjacent Nissl-stained sections. Each row of drawings is from a different experiment (identity given on the upper left end) described in the text.

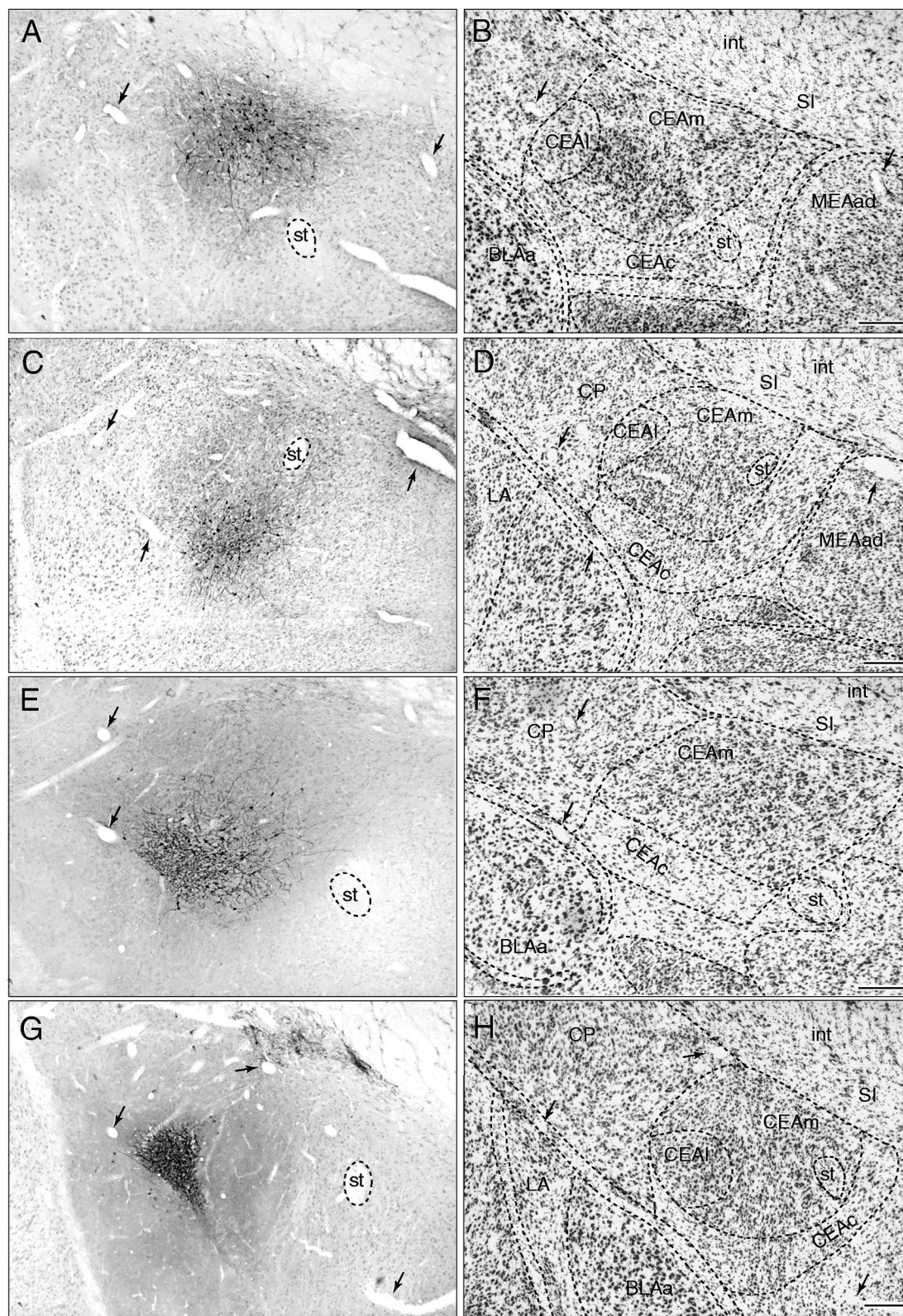


Fig. 5. Photomicrographs of PHAL injection sites in various regions of the central amygdalar nucleus. Each injection site (A,C,E,G) is accompanied by a photomicrograph of the same region as seen in the caudally adjacent Nissl-stained section. A,B: injection in the medial part of the central nucleus (experiment #2, see Fig. 4); C,D: injection in ventral regions of the capsular central nucleus (experiment #94, see Fig. 4); E,F: injection in lateral regions of the capsular central nucleus (experiment #84, see Fig. 4); and G,H: injection in the region of the caudoputamen (dorsal striatum) immediately dorsal to the central nucleus (experiment #91, see Fig. 4), a region that we had earlier [100] thought of as a dorsal region of the central nucleus. All scale bars=200 μ m.

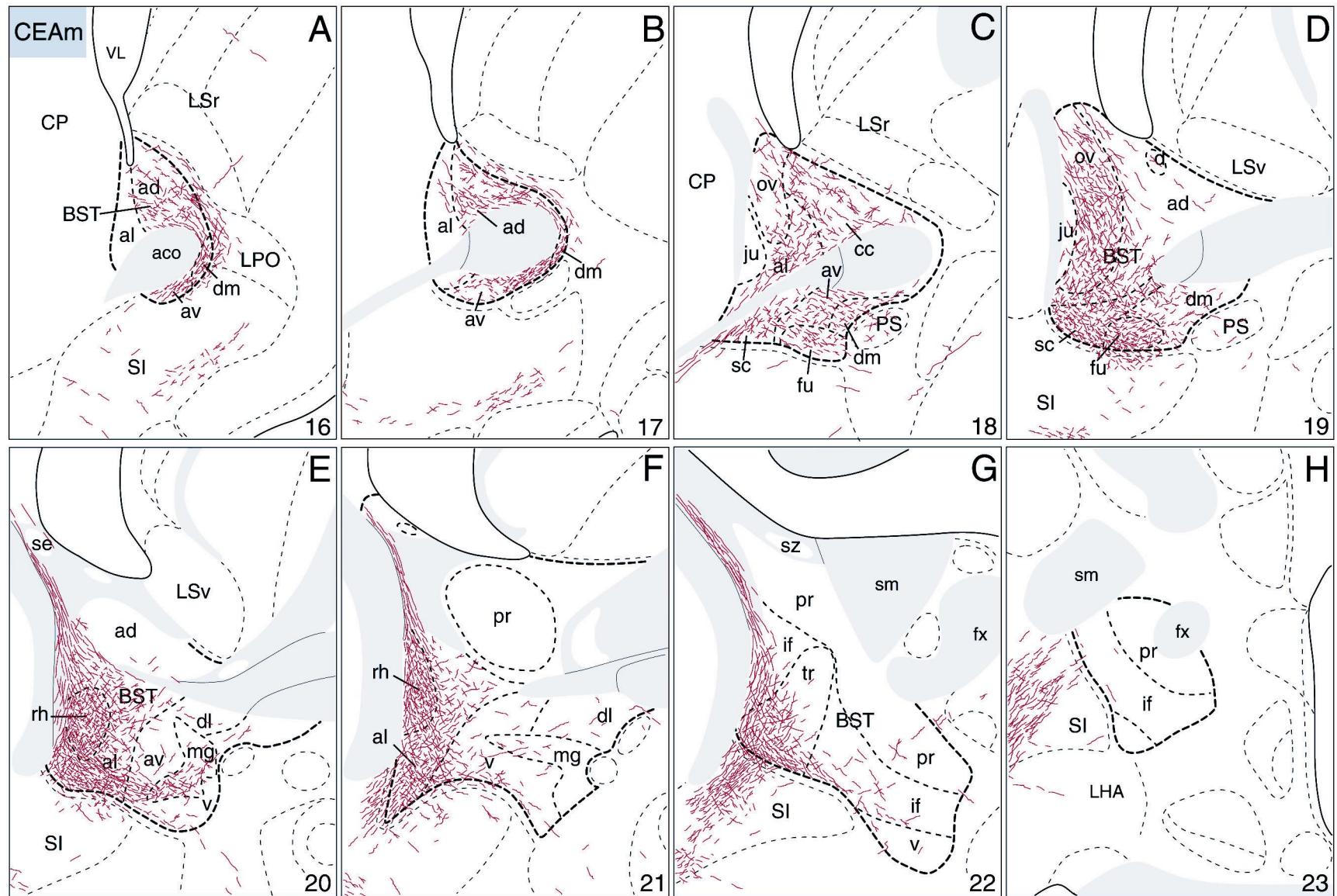


Fig. 6. Distribution of PHAL-labeled projections (red) from the medial part of the central amygdalar nucleus to the BST. The results of experiment #2 were plotted onto a series of rat brain atlas templates [100], arranged from rostral (A, atlas level 16) to caudal (H, atlas level 23).

the rhomboid nucleus is the most heavily innervated, whereas the rostral end of the anterolateral area, and the juxtacapsular nucleus, are virtually free of PHAL labeling (Fig. 6A–D). The medial central nucleus also provides moderate to dense inputs to the rostral part and central core of the anterodorsal area, the rostral part of the anteroventral area, the dorsomedial nucleus, and rostral regions of the magnocellular nucleus (Fig. 6A–E). Only scattered anterogradely labeled fibers were observed in other parts of the anterior division of the BST, including caudal regions of the anterodorsal area, caudal regions of the anteroventral area, the dorsolateral nucleus, and caudal regions of the dorsomedial and magnocellular nuclei (Fig. 6D–F).

PHAL-labeled axons enter the posterior division of the BST from both the stria terminalis and ansa peduncularis, and a moderate number of terminal boutons and boutons-of-passage were observed in the most lateral regions of the transverse nucleus (Fig. 6G). Labeled axons were also observed in lateral regions of the interfascicular nucleus, although most of them appear to be fibers-of-passage because they display very few boutons. The principal nucleus is free of anterograde labeling (Fig. 6G–H).

Previous anterograde and retrograde tracer studies [18,51,59,115] indicated that the central nucleus projects to the lateral edge of the BST. However, we found that the medial central nucleus also projects to the medial group of the anterior division (including the anterodorsal and anteroventral areas, and the dorsomedial and magnocellular nuclei), which is corroborated in a general way by the retrograde tracer results of Sun et al. [97]. They reported retrograde labeling in the medial central nucleus after tracer injections in the ‘anteromedial BST’ (which appears to include rostral regions of our anteroventral area and the dorsomedial nucleus) and into the ‘posteromedial BST’ (which appears to include caudal regions of our anteroventral area and the magnocellular nucleus).

4.1.2. From the lateral part of the central nucleus

The overall projections from this cell group have been described previously, along with the relevant earlier literature [76]; we have chosen from this study experiment CEAl#12 (Figs. 4 and 5) to show in detail how the BST is innervated (Figs. 3 and 7). In short, the lateral central nucleus innervates densely only three parts of the BST: the oval and fusiform nuclei, and the caudoventral tip of the anterolateral area (Fig. 7C–F). A few PHAL-labeled axons with boutons were also observed in rostral regions of the anterodorsal area, subcommissural zone, and rhomboid nucleus (Fig. 7A–F), whereas other parts of the BST contained at most a scattered labeled axon here and there.

4.1.3. From the capsular part of the central nucleus

Three experiments (CEAc#84, 91, and 94) were chosen to display projections associated with the capsular central nucleus. The ventral region of the capsular central nucleus as defined here corresponds approximately to the ventral

lateral capsular division of the central nucleus of Cassell et al. [17,18], and it was selectively labeled in experiment CEAc#94 (Figs. 4 and 5). PHAL-labeled axons from the injection site in this experiment coursed through both the stria terminalis and ansa peduncularis to reach the BST, where its innervation pattern was generally similar to that from the medial central nucleus, although the relative density of terminal fields differed (Figs. 3 and 8). The ventral capsular part of the central nucleus projects even more densely than the medial central nucleus to the caudal anterolateral area and subcommissural zone (Figs. 8C–F and 12D), and the fusiform and rhomboid nuclei are also densely innervated (Figs. 8C–F and 12D). In contrast, whereas the oval nucleus is heavily innervated by the medial and lateral parts of the central nucleus, it receives only a light projection from the ventral capsular part of the central nucleus (Fig. 8C,D). The ventral capsular part of the central nucleus projects more densely than the medial central nucleus to the following regions: rostral anterolateral area, rostral and central core of the anterodorsal area, and entire anteroventral area, including the dorsomedial and magnocellular nuclei (see Fig. 12A,D,G). Two other incidental observation in this experiment should be mentioned. First, a massive projection to the medial part of the central nucleus was labeled, whereas, in contrast, virtually no fibers could be detected in the dorsal vagal complex and hindbrain reticular formation.

The PHAL injection in experiment CEAc#84 (Figs. 4 and 5) selectively labeled what we now refer to as the lateral region of the capsular central nucleus [74], following other authors [18,57]. The vast majority of labeled axons here reach the BST via the ansa peduncularis. It is obvious from Figs. 3 and 9 that the lateral region generates a considerably more restricted input to the BST than the ventral region of the capsular central nucleus. Its only clear terminal fields are in the subcommissural zone and caudal region of the anterolateral area (Fig. 9D–F). A few branching axons with boutons were observed in the fusiform and rhomboid nuclei (Fig. 9C–E), and scattered apparent fibers-of-passage were seen here and there (e.g., in the transverse nucleus). Like the ventral region of the capsular central nucleus, the lateral region projects very densely to the medial central nucleus, but little if at all to the hindbrain.

What we have previously indicated as the dorsal region of the capsular central nucleus [100] was injected selectively in experiment CEAc#91 (Figs. 4 and 5). To our surprise, there were no labeled projections to the BST — or to the substantia innominata and autonomic-related cell groups in the brainstem — and only a very light projection to the medial central nucleus. Instead, clear terminal fields were labeled in the caudoventral globus pallidus and caudolateral substantia nigra. This evidence suggests that the cytoarchitectonically distinct dorsal region of the capsule as defined originally by McDonald [57] is more closely related to the dorsal striatum than to the central

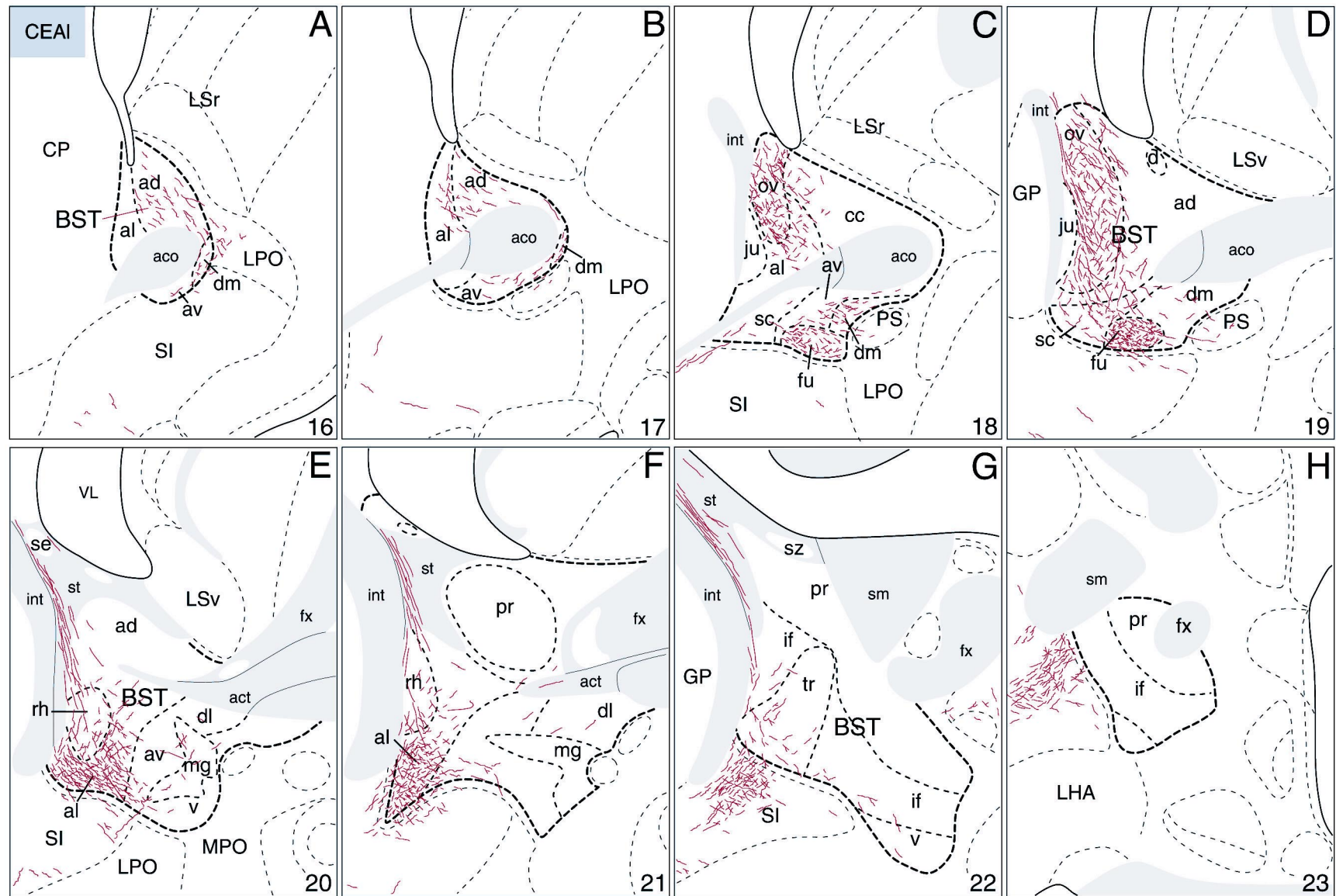


Fig. 7. Distribution of PHAL-labeled projections (red) from the lateral part of the central amygdalar nucleus to the BST. The results of experiment #12 are plotted as in Fig. 6.

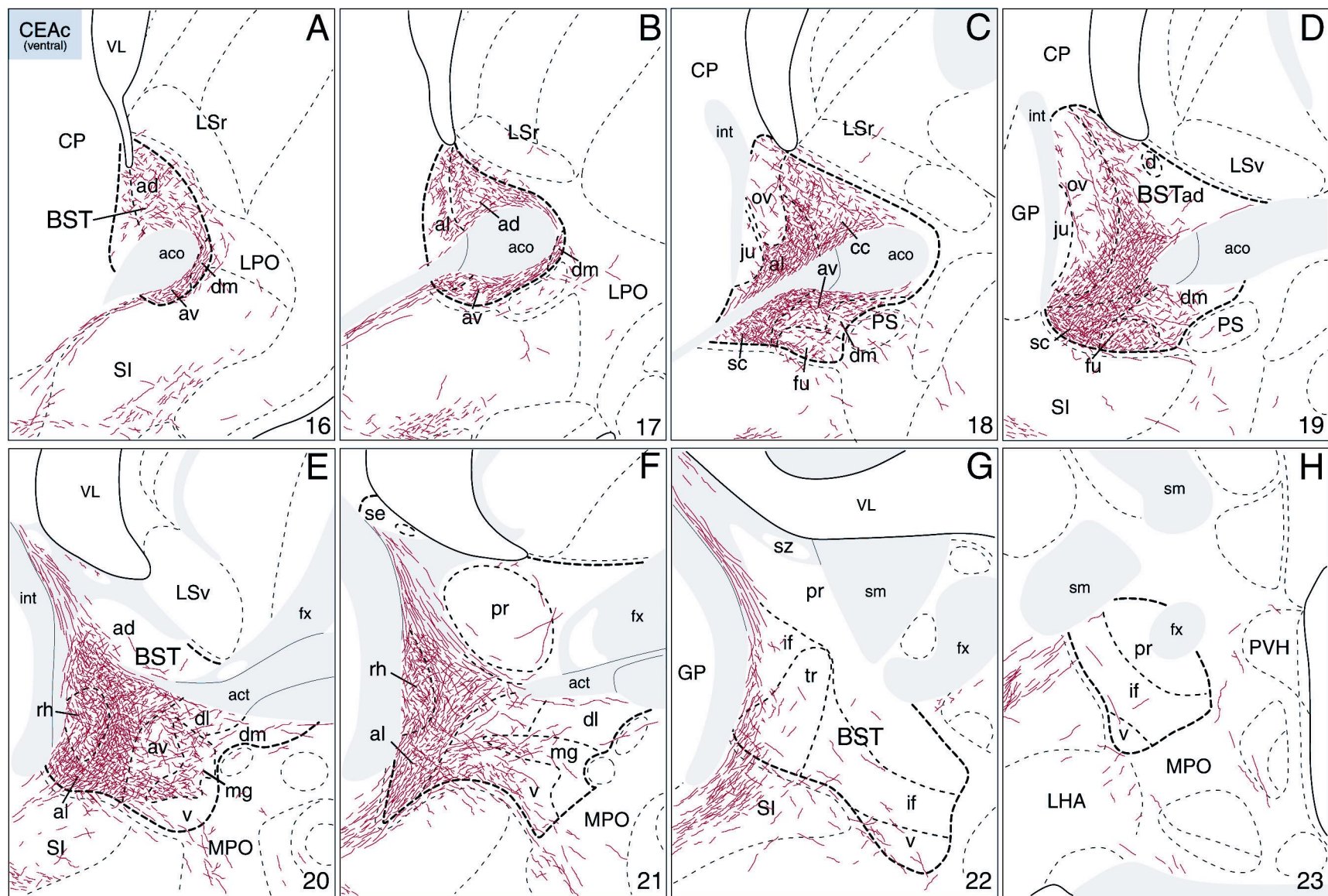


Fig. 8. Distribution of PHAL-labeled projections (red) from ventral regions of the capsular central amygdalar nucleus to the BST. The results of experiment #94 are plotted as in Fig. 6.

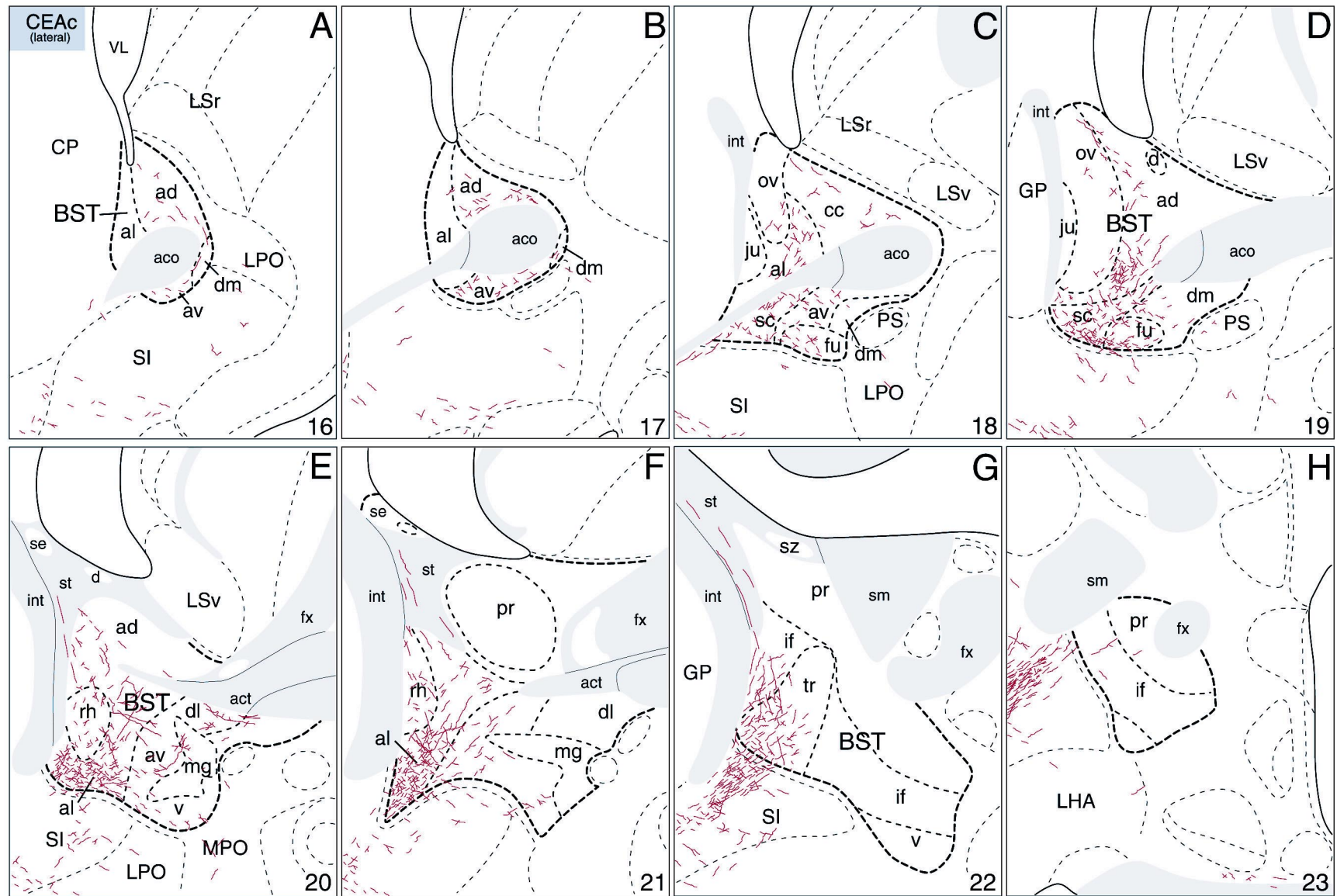


Fig. 9. Distribution of PHAL-labeled projections (red) from lateral regions of the capsular central amygdalar nucleus to the BST. The results of experiment #84 are plotted as in Fig. 6.

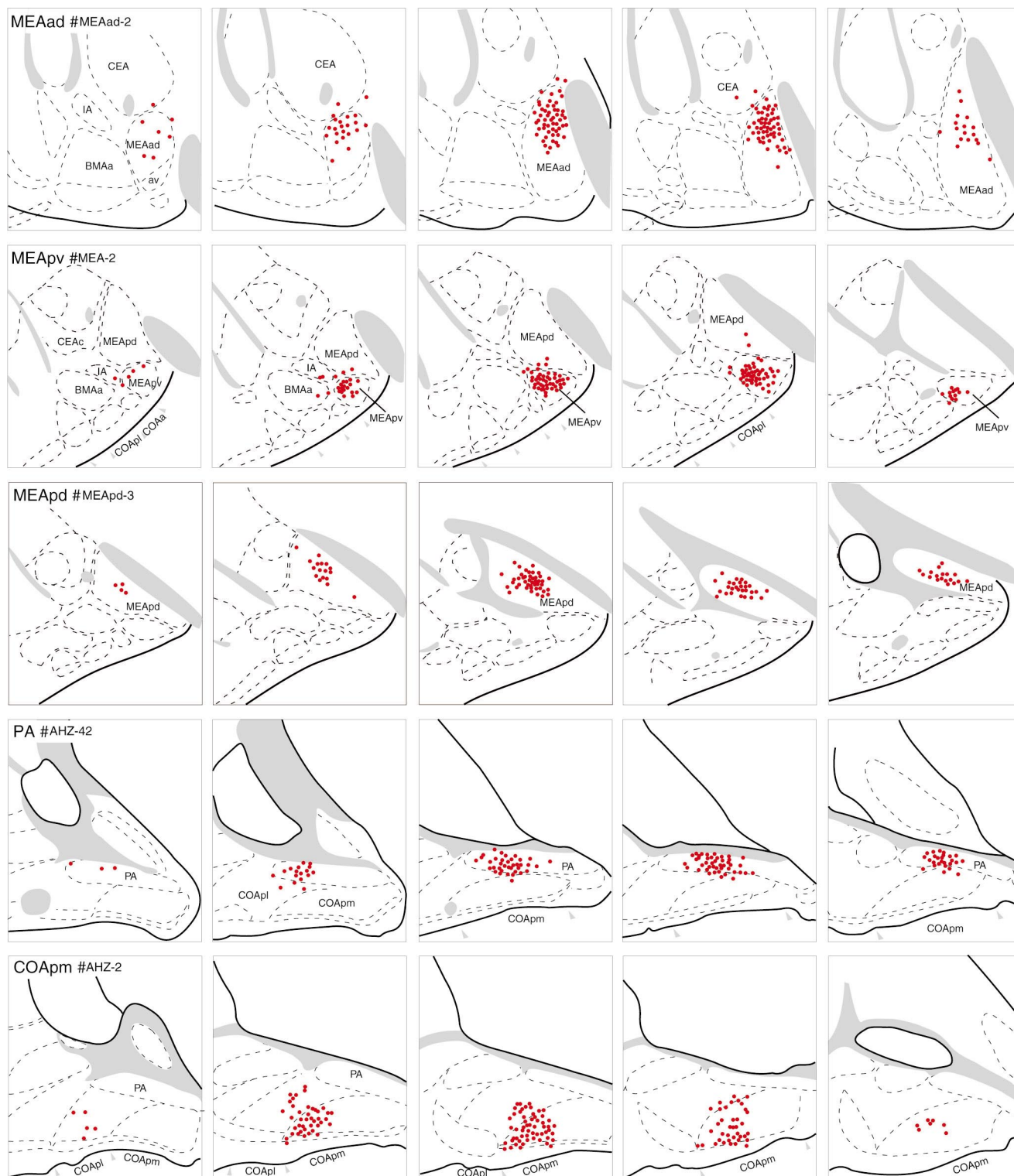


Fig. 10. PHAL injection sites involving various different regions of the amygdala associated particularly with the accessory olfactory system (the medial, posterior, and posteromedial cortical nuclei). Labeled neurons are plotted as described in Fig. 4.

amygdalar nucleus, as suggested already by Price et al. [78], who referred to it on cytoarchitectonic and comparative grounds as the caudoventral portion of the putamen. Paxinos and Watson [72] refer to this general region as the amygdalostratial transition area.

Projections from the capsular central nucleus to the BST have not been examined previously with anterograde tracing methods. The only relevant corroboration of our results comes from experiments with retrograde tracer injections in Bleier's [10] lateral division of the BST,

which labeled neurons in ventral and lateral regions of the capsular central nucleus [18,97]. In addition, projections from the capsular part to the medial part of the central nucleus have been reported [17,46], as have projections from the 'dorsal region of the capsular part' to the globus pallidus and substantia nigra [35,88,91].

4.2. Projections from the pheromonal system

By far the most densely innervated targets of the accessory olfactory bulb are the posteromedial cortical nucleus of the amygdala (a cortical area) and the medial nucleus of the amygdala (part of the caudal striatum), just as the main olfactory bulb massively innervates the posterolateral cortical nucleus and olfactory tubercle (part of the ventral striatum) [85,107]. In addition, it has been suggested that one other component of the amygdala, the posterior nucleus, is part of the claustral complex or cortical subplate most closely associated with the posterior cortical nucleus [107]. We shall now describe projections to the BST from the three parts of the amygdala most closely associated with the pheromonal system (Fig. 1): the medial, posteromedial cortical, and posterior nuclei.

4.2.1. From the medial nucleus

The overall projections from the anterodorsal, posteroventral, and posterodorsal parts of the medial nucleus have already been described in detail, along with the relevant earlier literature [14]. We have selected the best experiment involving each part (Fig. 10) to illustrate the precise innervation pattern in the BST. To summarize, projections to the BST from the medial nucleus are very different from those arising in the central nucleus (Fig. 3). All three parts of the medial nucleus project very heavily to the posterior division of the BST, and less heavily to the medial group of the anterior division. In contrast, the lateral group of the anterior division, which is massively innervated by the central nucleus, is essentially avoided by projections from the medial nucleus.

The anterodorsal part — experiment #MEAad-2, Fig. 10. Many PHAL-labeled axons can be followed from the injection site through the stria terminalis and ansa peduncularis to converge on the posterior division of the BST where they generate extremely dense terminal boutons and boutons-of-passage in the transverse and interfascicular nuclei, and in the caudal pole of the principal nucleus (Figs. 11F, G and 12H). More rostral regions of the principal nucleus are only moderately to lightly innervated (Figs. 11F, G and 12H). In the anterior division of the BST, the central core and caudal end of the anterodorsal area are densely innervated (Figs. 11B–E and 12E), whereas the rostral end of the anterodorsal area is only lightly innervated (Figs. 11A,B and 12B). The anterodorsal medial nucleus also densely innervates the anteroventral area, as well as the dorsomedial, dorsolateral, magnocellular, and ventral nuclei (Figs. 11A–F and 12E). The

anterolateral area and subcommissural zone are lightly to moderately innervated, whereas the juxtacapsular, oval, fusiform, and rhomboid nuclei are virtually free of labeled axons (Figs. 11A–F and 12B,E).

The posteroventral part — experiment #MEA-2, Fig. 10. Compared to experiments involving the anterodorsal part of the medial nucleus, considerably more labeled axons travel through the stria terminalis as compared to the ansa peduncularis on their way to the BST from the posteroventral part (Fig. 13G). In the posterior division of the BST, the pattern of terminal distribution was, however, similar. The posteroventral part of the medial nucleus generates a tremendous number of boutons in the interfascicular and transverse nuclei, and in the caudal end of the principal nucleus, whereas the rest of the principal nucleus is only lightly innervated (Fig. 13F–H). In the anterior division of the BST, the caudal end of the anterodorsal nucleus is densely innervated (Fig. 13D,E) whereas more rostrally, the central core and rostral end receive only a light to moderate input (Fig. 13A–C). Additional regions that are lightly to moderately innervated include the caudal end of the anteroventral area, and the dorsolateral, dorsomedial, magnocellular, and ventral nuclei (Figs. 3 and 13E,F).

The posterodorsal part — experiment #MEApd-3, Fig. 10. The vast majority of axons from the posterodorsal part of the medial nucleus reach the BST via the stria terminalis as compared to the ansa peduncularis (Fig. 14E–G). Remarkably, the posterodorsal part massively innervates the principal nucleus of the posterior division, whereas the transverse and interfascicular nuclei and the caudal end of the principal nucleus (all three of which are massively innervated by the anterodorsal and posteroventral parts of the medial nucleus) receive only very light projections (Figs. 3, 12I and 14F–H). In the anterior division of the BST, the posterodorsal medial nucleus innervates most densely caudal regions of the anterodorsal area (Figs. 12F and 14D), whereas the central core of the anterodorsal area receives a moderate input, and the rostral end of the anterodorsal area is only very lightly innervated (Figs. 3, 12C and 14A–C). In addition, the magnocellular and dorsolateral nuclei contain small to moderate numbers of branching axons and terminal boutons labeled with PHAL (Figs. 3 and 14E,F).

Leaving aside differences in nomenclature, our results are in general agreement with those reported for the male Syrian hamster [19,34].

4.2.2. From the posterior nucleus

The overall projections from the posterior nucleus have been described previously, along with the earlier literature, where it has been referred to variously as the cortico-amygdaloid transition area, posterior part of the medial nucleus, amygdalo-hippocampal transition area, posteromedial basal nucleus, and amygdalo-hippocampal area [12]. The injection site in the experiment chosen for the

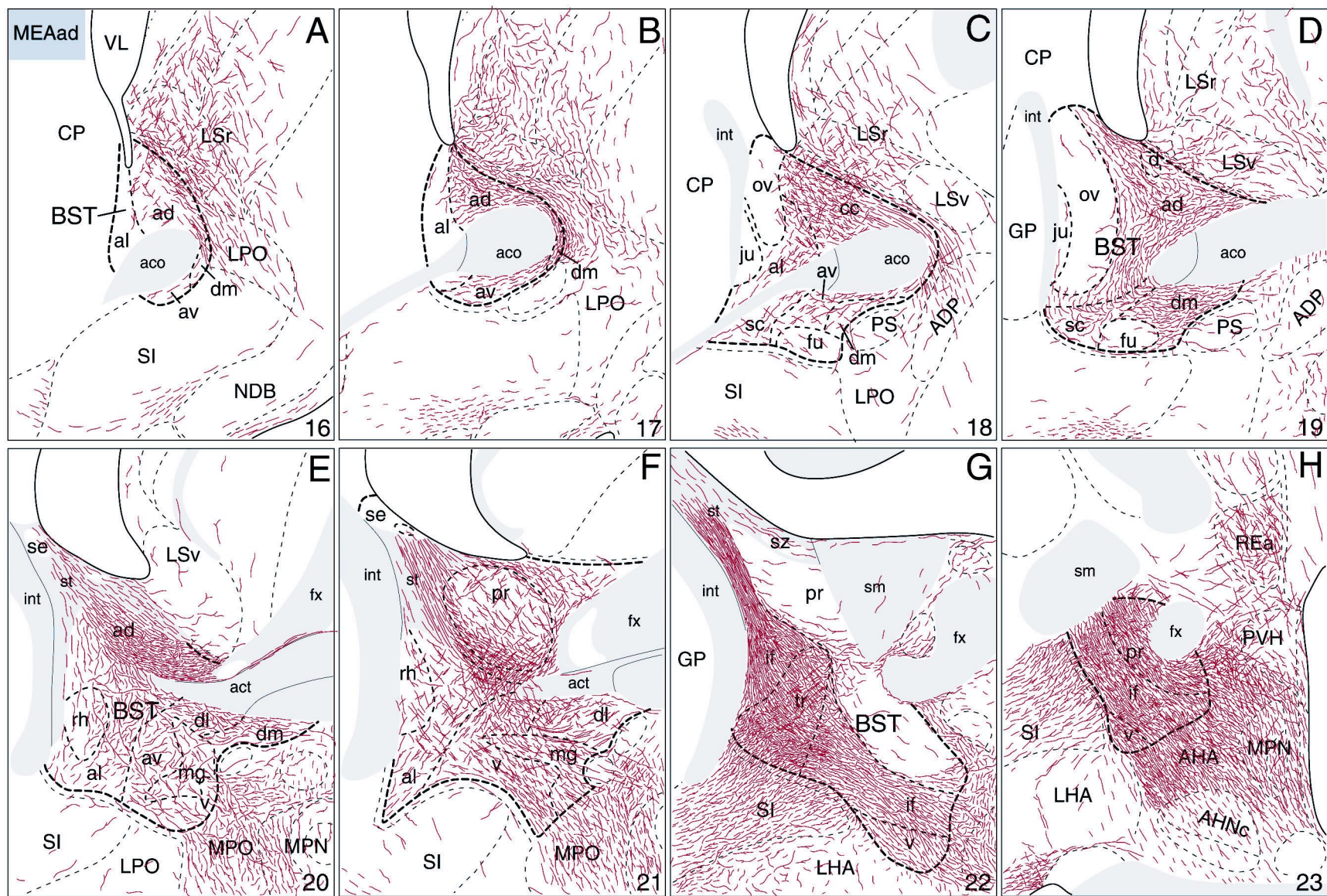


Fig. 11. Distribution of PHAL-labeled projections (red) from the anterodorsal part of the medial amygdalar nucleus to the BST. The results of experiment #MEAad-2 are plotted as in Fig. 6.

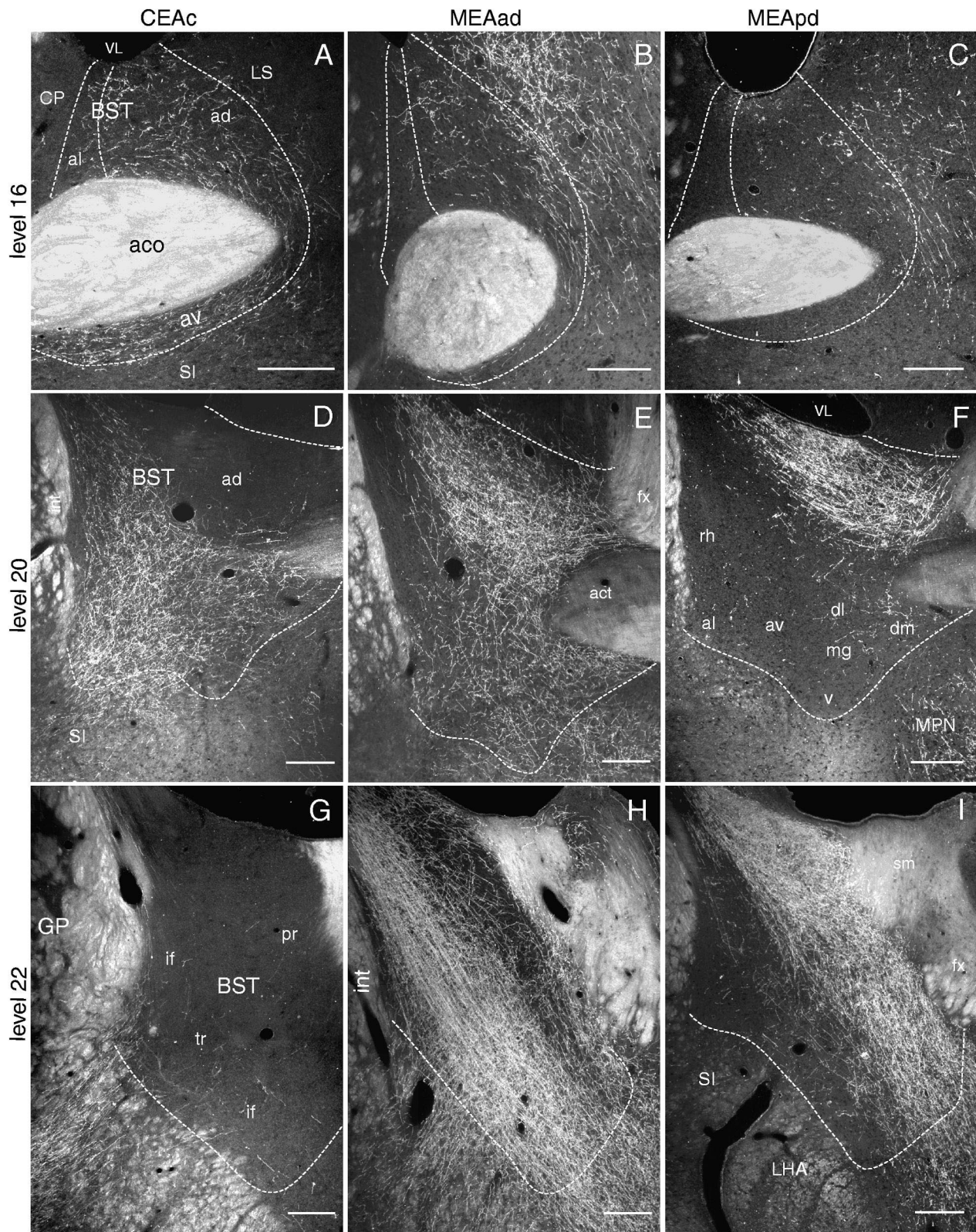


Fig. 12. Photomicrographs (darkfield illumination) comparing PHAL-labeled inputs to BST from ventral regions of the capsular central nucleus (A,D,G), anterodorsal medial nucleus (B,E,H), and posterodorsal medial nucleus (C,F,I). Results in transverse sections are illustrated at three rostrocaudal levels, corresponding approximately to atlas [100] levels 16, 20, and 22. Illustrations for the capsular central nucleus are from experiment #94 (Figs. 4, 5 and 8), for the anterodorsal medial nucleus from experiment #MEAad-2 (Figs. 10 and 11), and for the posterodorsal medial nucleus from experiment #MEApd-3 (Figs. 10 and 14). All scale bars=200 μ m.

present detailed analysis was almost entirely confined to the nucleus, although it did spread to label a few neurons in the adjacent posterior cortical nucleus (Fig. 10, #AHZ-42).

The projection of the posterior nucleus upon the BST is very similar to that from the posterodorsal part of the medial nucleus. The projection courses mostly through the stria terminalis as opposed to the amygdalofugal component of the ansa peduncularis, and its major terminal fields in the BST include the principal nucleus of the posterior division, and the anterodorsal area of the anterior division (Figs. 3 and 15A–E). Interestingly, it also innervates densely the dorsal nucleus — a tiny cell group assigned to the posterior division (Fig. 15D,E). Other regions of the BST contain only stray fibers, except for the magnocellular nucleus, which is lightly innervated (Fig. 15E,F).

4.2.3. From the posteromedial cortical nucleus

The overall projections of this cortical subfield have been described previously, along with the relevant previous literature [12]. The injection site in experiment #AHZ-2, which was centered in layer 2 but labeled neurons in layers 1 and 3 as well, is shown in Fig. 10. It also spread to label a few neurons in layer 3 of the posterolateral cortical nucleus.

A great majority of projections from the posteromedial cortical nucleus to the BST travel through the stria terminalis as opposed to the ansa peduncularis (Fig. 16E–H), and like the anterodorsal and posteroventral parts of the medial nucleus they preferentially target the transverse and interfascicular nuclei in the posterior division (Figs. 3 and 16G), and the anterodorsal area in the anterior division (Fig. 16A–E). However, the caudal ends of the interfascicular and principal nuclei, which are heavily innervated by the anterodorsal and posteroventral parts of the medial nucleus, receive only a light input from the posteromedial cortical nucleus (Fig. 16H). Aside from a few branched axons and boutons in the dorsomedial nucleus of the anterior division (Figs. 3 and 16F–H), the rest of the BST is without significant input from the posteromedial cortical nucleus.

Unlike most other cell groups associated with the amygdala, the posteromedial cortical nucleus generates a substantial projection to the contralateral BST. Thus, a moderate number of axons in the stria terminalis cross the midline near the dorsal and ventral borders of the anterior commissure (Fig. 16D–F) to innervate the contralateral interfascicular and transverse nuclei before extending caudally through the stria terminalis to the contralateral amygdala, where they seem to end in the medial and posterior cortical nuclei.

4.3. Projections from the main olfactory system

All PHAL injection sites from experiments used to

illustrate projections to the BST from amygdalar cell groups particularly closely associated with the main olfactory system (Fig. 1) are illustrated in Fig. 17. Based on the distribution of these projections, the main olfactory-related cell groups fall into two groups (Fig. 3). One group includes the anterior amygdalar area, the anterior cortical nucleus and anterior basomedial nucleus, and the postpiriform transition area and posterior basolateral nucleus. Like the central nucleus of the amygdala, these cell groups preferentially innervate the lateral group of the anterior BST. In contrast, the other group includes the piriform–amygdalar area and posterior basomedial nucleus, and the posterolateral cortical nucleus. Like the three amygdalar cell groups most closely associated with the accessory olfactory system, they preferentially innervate the posterior BST.

4.3.1. From the anterior amygdalar area

The injection site in experiment #69 labeled many neurons in the anterior area, but spread to include a few neurons in adjacent cell groups, including the medial part of the central nucleus (Fig. 17). Almost all labeled axons to the BST in this brain course ventrally through the ansa peduncularis, rather than dorsally through the stria terminalis (Fig. 18G,H). In addition, a few labeled axons enter the rostral ends of the anteroventral area and subcommissural zone of the BST from the region of the striatal fundus surrounding the temporal limb of the anterior commissure.

The anterior amygdalar area innervates the BST in a pattern reminiscent in some ways of that from the medial part of the central nucleus (Figs. 3 and 18). For example, both cell groups innervate densely certain regions of the lateral group of the anterior division, including the anterolateral area, rhomboid nucleus, and subcommissural zone (Figs. 3 and 18B–F); and they both moderately innervate the rostral end and central core of the anterodorsal area, the anteroventral area, and the dorsomedial nucleus (Figs. 3 and 18A–E). In contrast, the oval and fusiform nuclei are heavily innervated by the medial part of the central nucleus, but receive very little input from the anterior amygdalar area (Fig. 18C,D). Finally, the anterior area sends moderate inputs to lateral regions of the transverse nucleus (Fig. 18G), and light inputs to the interfascicular and principal nuclei (Fig. 18G,H), and the rostral end of the anterolateral area (Fig. 18A).

There is very little relevant work in the literature on the projections of the anterior amygdalar area. Our results are in general agreement with the retrograde tracer results described by McDonald [58,59].

4.3.2. From the anterior basomedial nucleus

The overall projections from this nucleus have been described, along with the relevant literature [75]. To illustrate in detail its input to the BST we have chosen experiment #60 (Fig. 17). Fibers to the BST course

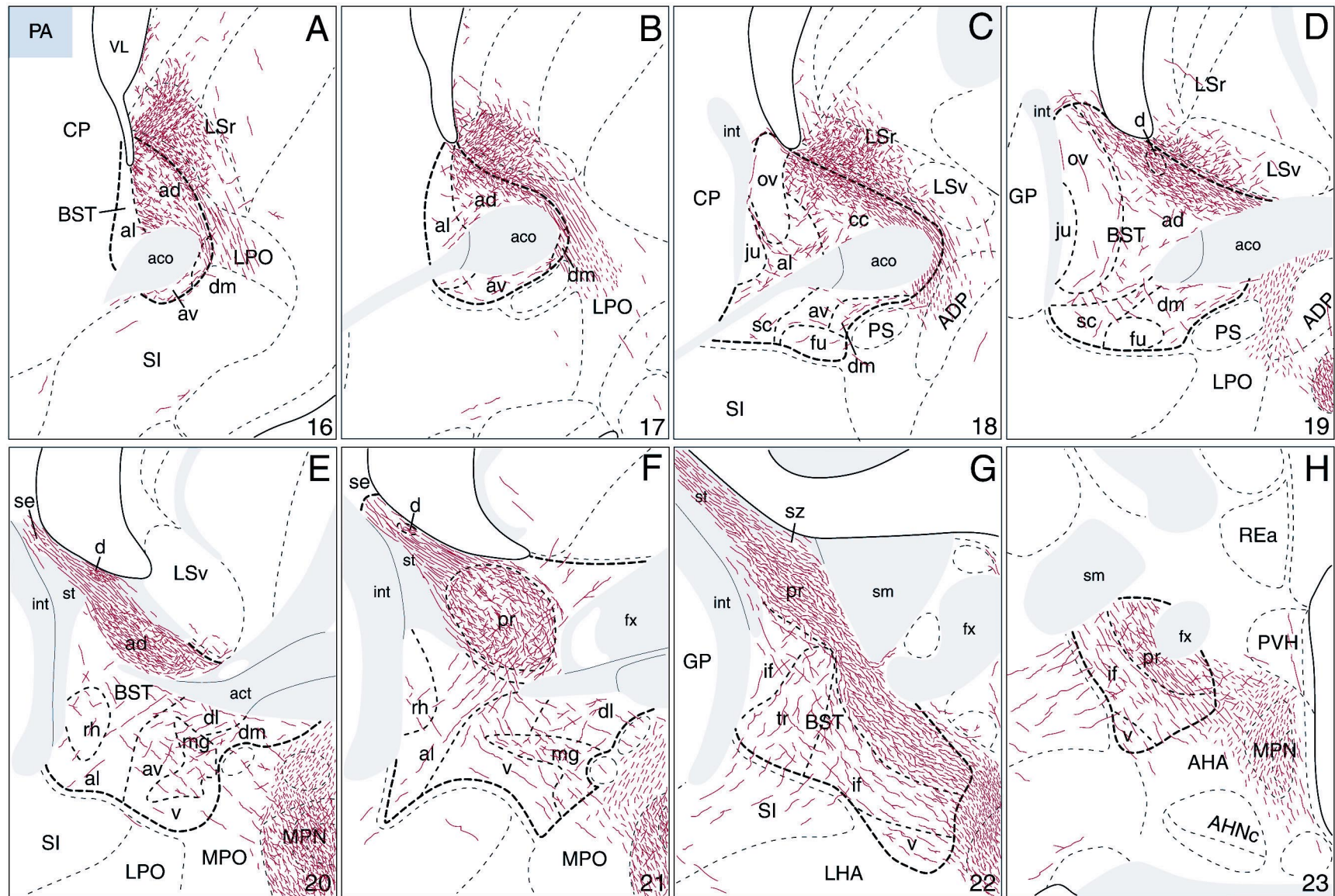


Fig. 15. Distribution of PHAL-labeled projections (red) from the posterior amygdalar nucleus to the BST. The results of experiment #AHZ-42 are plotted as in Fig. 6.

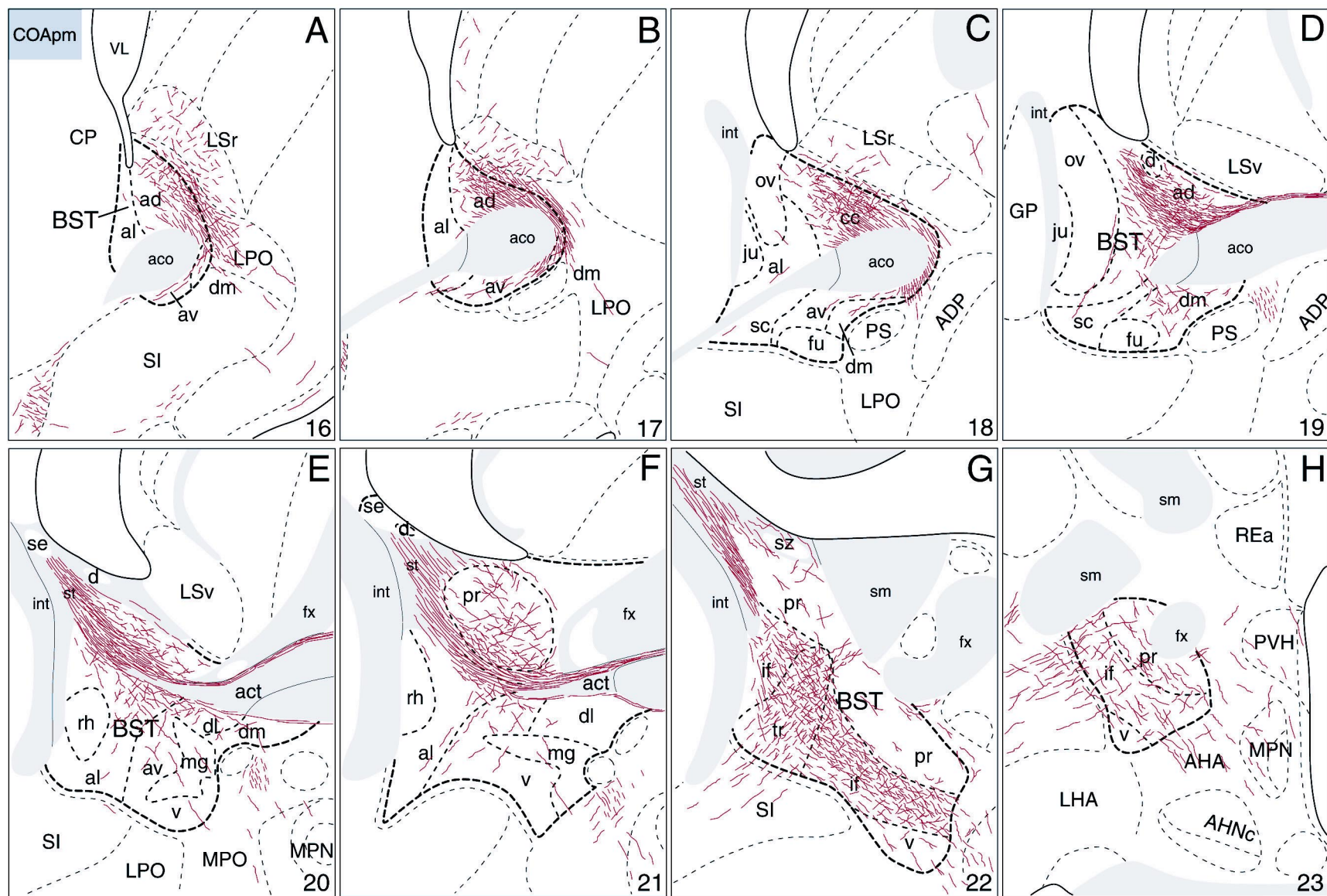


Fig. 16. Distribution of PHAL-labeled projections (red) from the posteromedial cortical amygdalar nucleus to the BST. The results of experiment #AHZ-2 are plotted as in Fig. 6.

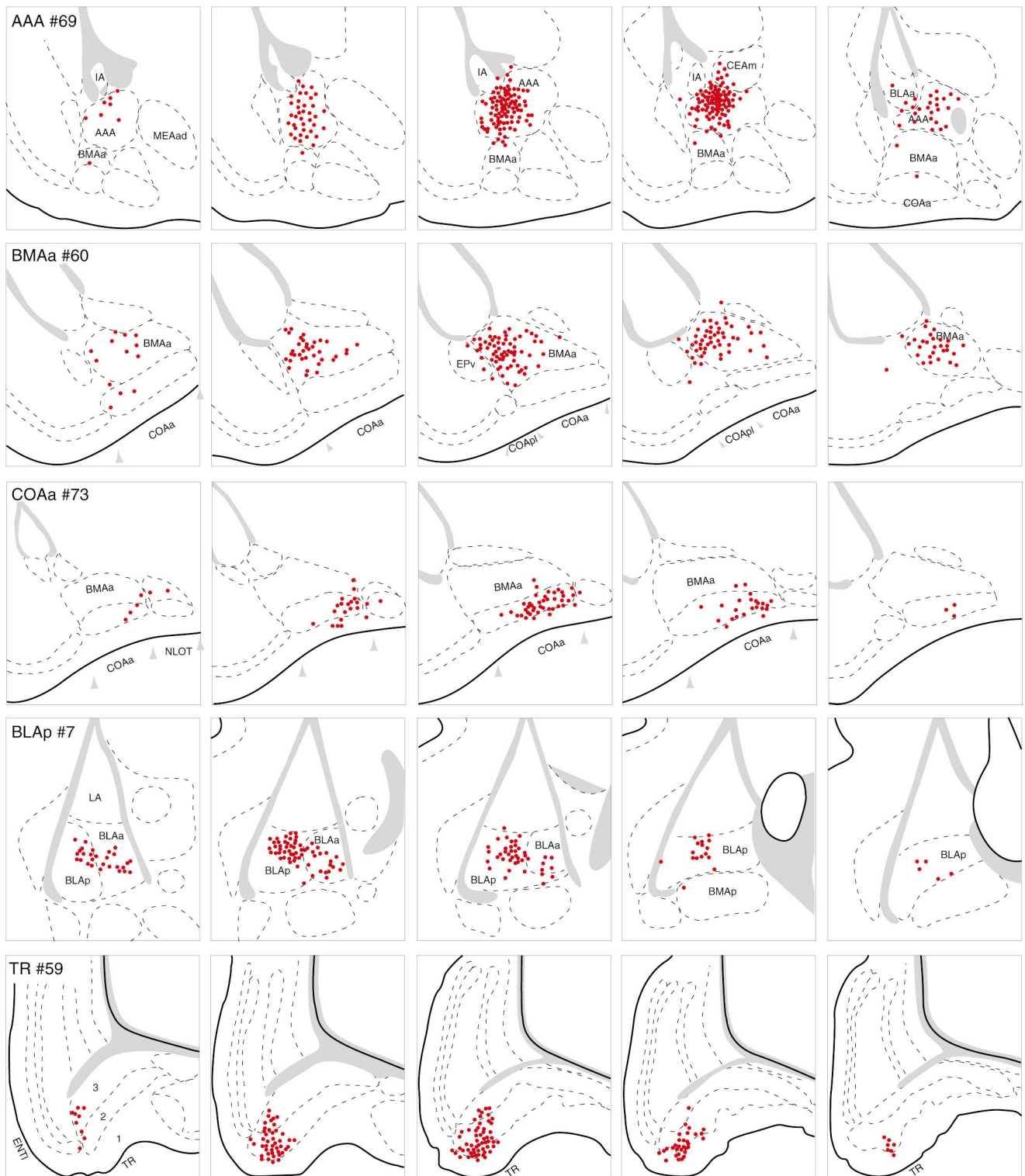


Fig. 17. PHAL injection sites involving various different regions of the amygdala associated particularly with the main olfactory system. Labeled neurons are plotted as described in Fig. 4.

through both the stria terminalis and ansa peduncularis (including a component near the temporal limb of the anterior commissure), and generate terminal fields throughout most of the anterior division (Figs. 3 and 19).

Extremely dense inputs are established in most of the anterolateral area, in the rhomboid nucleus, and in the subcommissural zone, whereas the oval and fusiform nuclei, and the rostral end and caudoventral tip of the

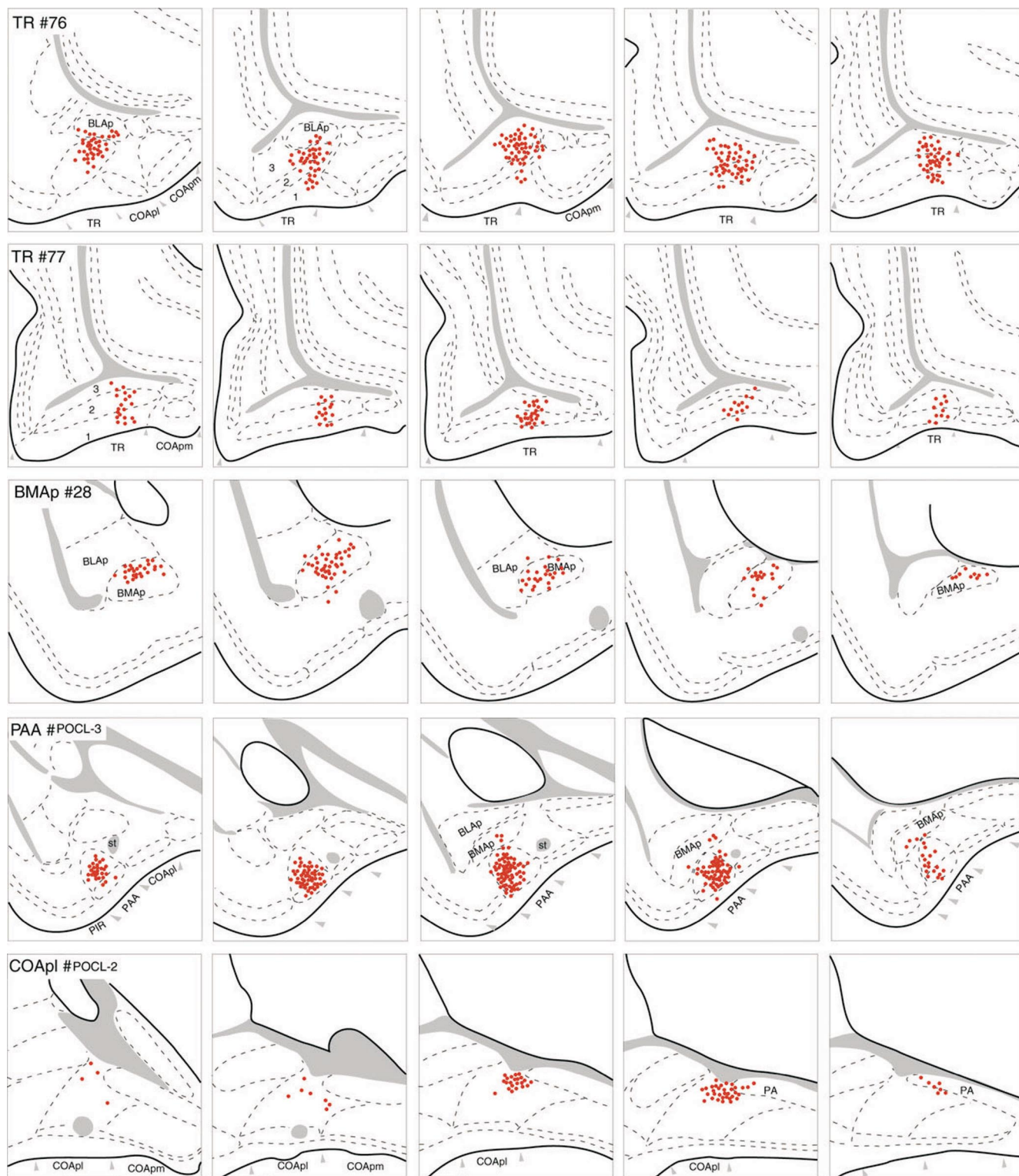


Fig. 17. (continued)

anterolateral area, receive only light to moderate inputs (Fig. 19C–F). Other regions of the BST that receive massive inputs include the rostral two-thirds of the anterodorsal area, the anteroventral area, the dorsomedial and

dorsolateral nuclei, dorsal regions of the ventral nucleus, lateral regions of the transverse nucleus, and the interfascicular nucleus. Other regions of the BST contain only an occasional labeled axon (Fig. 19A–H).

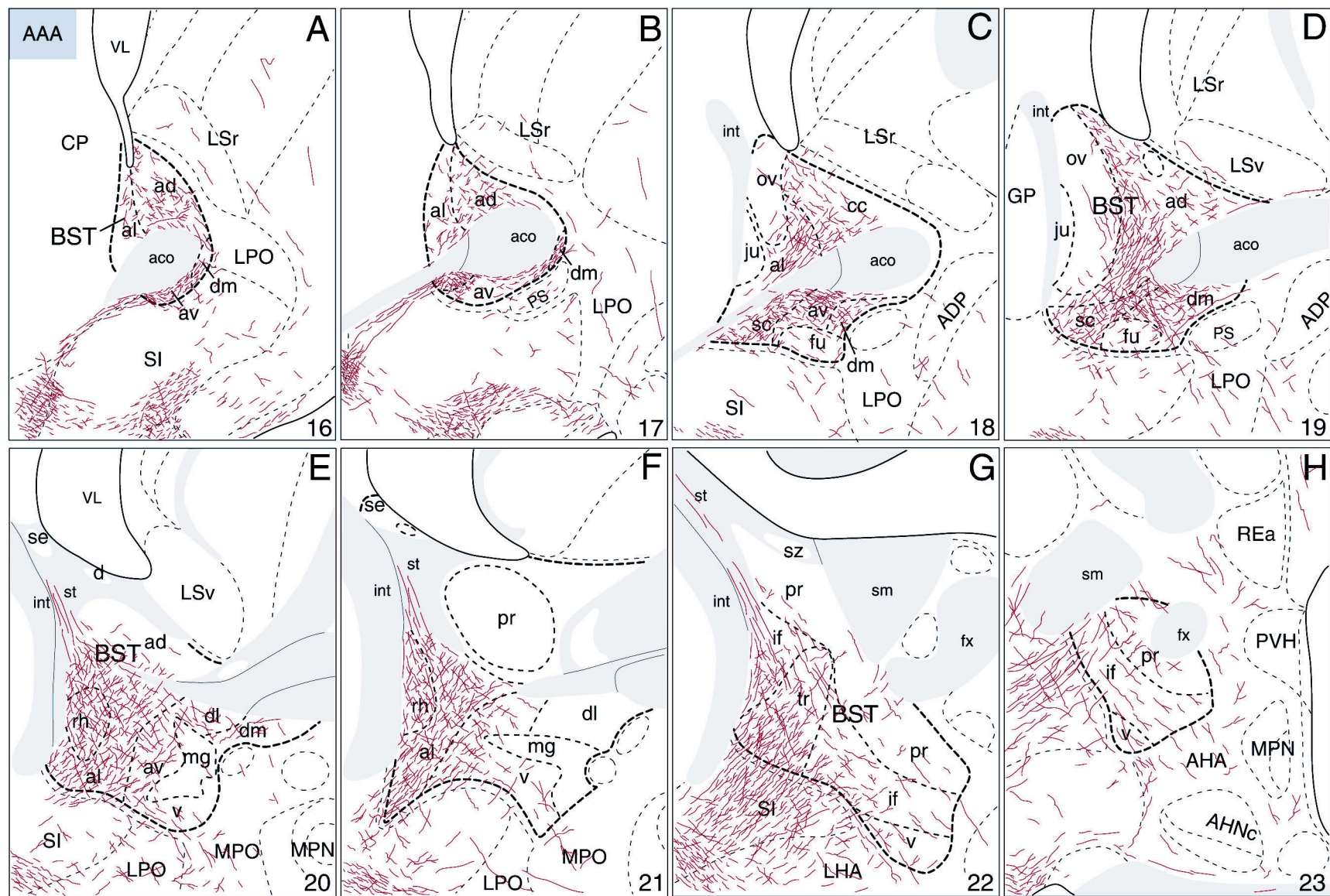


Fig. 18. Distribution of PHAL-labeled projections (red) from the anterior amygdalar area to the BST. The results of experiment #69 are plotted as in Fig. 6.

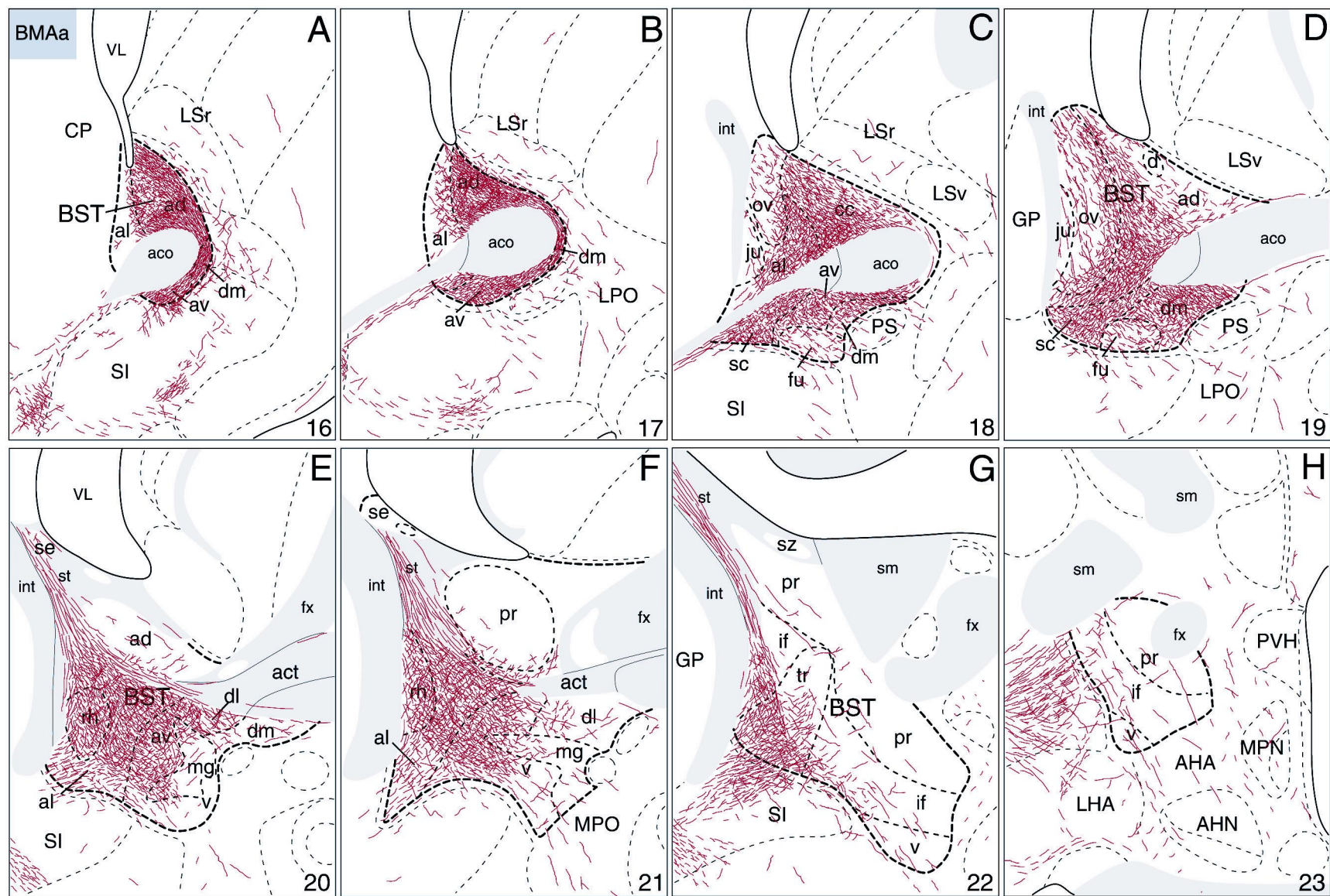


Fig. 19. Distribution of PHAL-labeled projections (red) from the anterior basomedial nucleus to the BST. The results of experiment #60 are plotted as in Fig. 6.

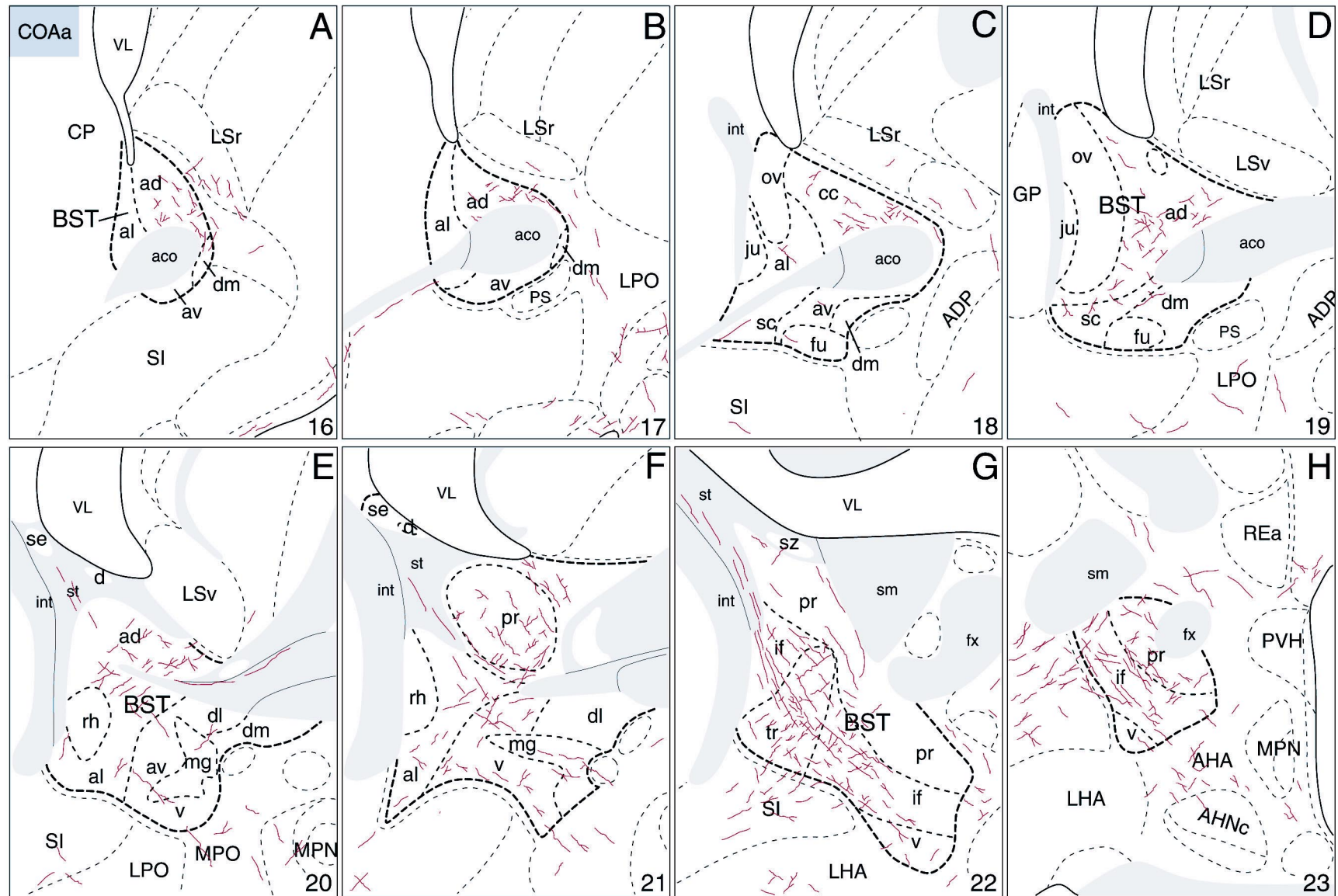


Fig. 20. Distribution of PHAL-labeled projections (red) from the anterior cortical amygdalar nucleus to the BST. The results of experiment #73 are plotted as in Fig. 6.

4.3.3. From the anterior cortical nucleus

This cortical area lies just superficial to the anterior basomedial nucleus, which some authors consider the deep layer of the anterior cortical nucleus (e.g. [78]), similar perhaps to the way the endopiriform nucleus lies deep to the piriform area [107]. The pattern of its overall projections has been described elsewhere, along with the relevant literature [75]. To illustrate its precise innervation of the BST, experiment #73 will be used. The injection site here (Fig. 17) was centered in the anterior cortical nucleus, with a few labeled neurons in the underlying anterior basomedial nucleus.

Axons from the anterior cortical nucleus course through both the stria terminalis and ansa peduncularis to innervate relatively lightly the BST (Figs. 3 and 20). A small number of PHAL-labeled fibers with boutons were observed in the anterodorsal area of the anterior division (Fig. 20A–E), and in the rostral principal nucleus, transverse nucleus, and interfascicular nucleus of the posterior division (Fig. 20F–H). Other regions of the BST are virtually free of anterograde labeling, except for an occasional fiber-of-passage.

4.3.4. From the posterior basolateral nucleus

The best PHAL injection of this cell group in our collection is in experiment #7 (Fig. 17). The only detectable spread of the injection site was to the adjacent anterior part of the basolateral nucleus. However, because injections centered in the latter do not label projections to the BST (Section 4.4), it would appear that experiment #7 is useful for clarifying posterior basolateral projections to the BST.

As shown in Fig. 21, the posterior basolateral nucleus sends fibers to the BST via both the dorsal and ventral routes. Like the medial part of the central nucleus, the posterior basolateral nucleus heavily innervates the caudal end of the anterolateral area, the rhomboid nucleus, and the subcommissural zone (Fig. 21C–F), whereas the oval and fusiform nuclei, which are heavily innervated by the medial central nucleus, receive only widely scattered axons from the posterior basolateral nucleus (Fig. 21C,D). Instead, the rostral end of the anterolateral area and the juxtacapsular nucleus, which are avoided by axons from the medial central nucleus, receive very dense inputs from the posterior basolateral nucleus (Fig. 21A–D). The latter also sends moderately dense inputs to a number of regions in the medial group of the anterior division of the BST, including the rostral two-thirds of the anterodorsal area, the dorsomedial nucleus, and dorsal regions of the ventral nucleus (Figs. 3 and 21A–F).

PHAL-labeled axons are also observed in ventrolateral regions of the transverse nucleus, and in the interfascicular nucleus, of the posterior BST, although fibers in the former display more boutons indicative of synapses (Fig. 21G). There are almost no labeled axons in the principal nucleus (Fig. 21F–H).

Krettek and Price [51] reported that ^3H -amino acid injections in either the anterior or posterior part of the basolateral nucleus produced transported label in their lateral but not medial division of the BST in rat and cat. Our results confirm a dense input to the lateral group of structures in the anterior division of the BST. However, we also labeled moderate inputs to several parts of the medial group of structures in the anterior division, including the anterodorsal and anteroventral areas and the dorsomedial nucleus. In a recent PHAL analysis, Shammah-Lagnado et al. [89] also observed projections from the posterior basolateral nucleus to rostromedial regions of the BST, in addition to its massive inputs to more lateral regions (see their Fig. 15). Finally, the results of retrograde tracer experiments support the conclusion that at least most projections to the BST from the basolateral nucleus arise in the posterior part [59,115].

4.3.5. From the postpiriform transition area

This main olfactory cortical area lies just superficial to the posterior basolateral nucleus, and is part of the more general periamygdalar cortex (Fig. 1). Our PHAL collection has three injections centered in this poorly understood, undoubtedly complex area (Fig. 17). In experiment #76 the injection site is centered in the rostromedial end of the postpiriform area, with involvement of both layers 2 and 3, as well as some neurons in the adjacent posterior basolateral nucleus. In experiment #59 the injection appears to be restricted entirely to layers 2 and 3 of the caudolateral postpiriform area. And in experiment #77 the PHAL injection is limited to caudomedial regions of the postpiriform area, mainly in layer 2. Projections to the BST from these three regions of the postpiriform area differed rather substantially, and so were mapped separately (Figs. 22–24) and summarized in Fig. 3.

In all three experiments a majority of labeled fibers reach the BST by coursing through the stria terminalis, although moderate numbers were observed in the ventral, ansa peduncularis pathway in experiment #76 (rostromedial). In experiment #59 (caudolateral) dense terminal fields were observed mainly in the oval and juxtacapsular nuclei (Fig. 22C,D), whereas in experiment #77 (caudomedial) the most obvious axonal branching and bouton production were in the anterodorsal area (Fig. 23A–D). In experiment #76 (rostromedial) extremely dense terminal fields were observed in the anterodorsal, anteroventral, and anterolateral areas; in the dorsomedial, juxtacapsular, oval, and rhomboid nuclei; and in the subcommissural zone (Figs. 3 and 24A–F). In this experiment, mostly what appear to be fibers-of-passage were observed in caudal regions of the anteroventral area, and in the fusiform, magnocellular, dorsolateral, and ventral nuclei. Almost all labeling in the posterior division of the BST in these experiments appears to be associated with fibers-of-passage. One exception was some labeled bouton-

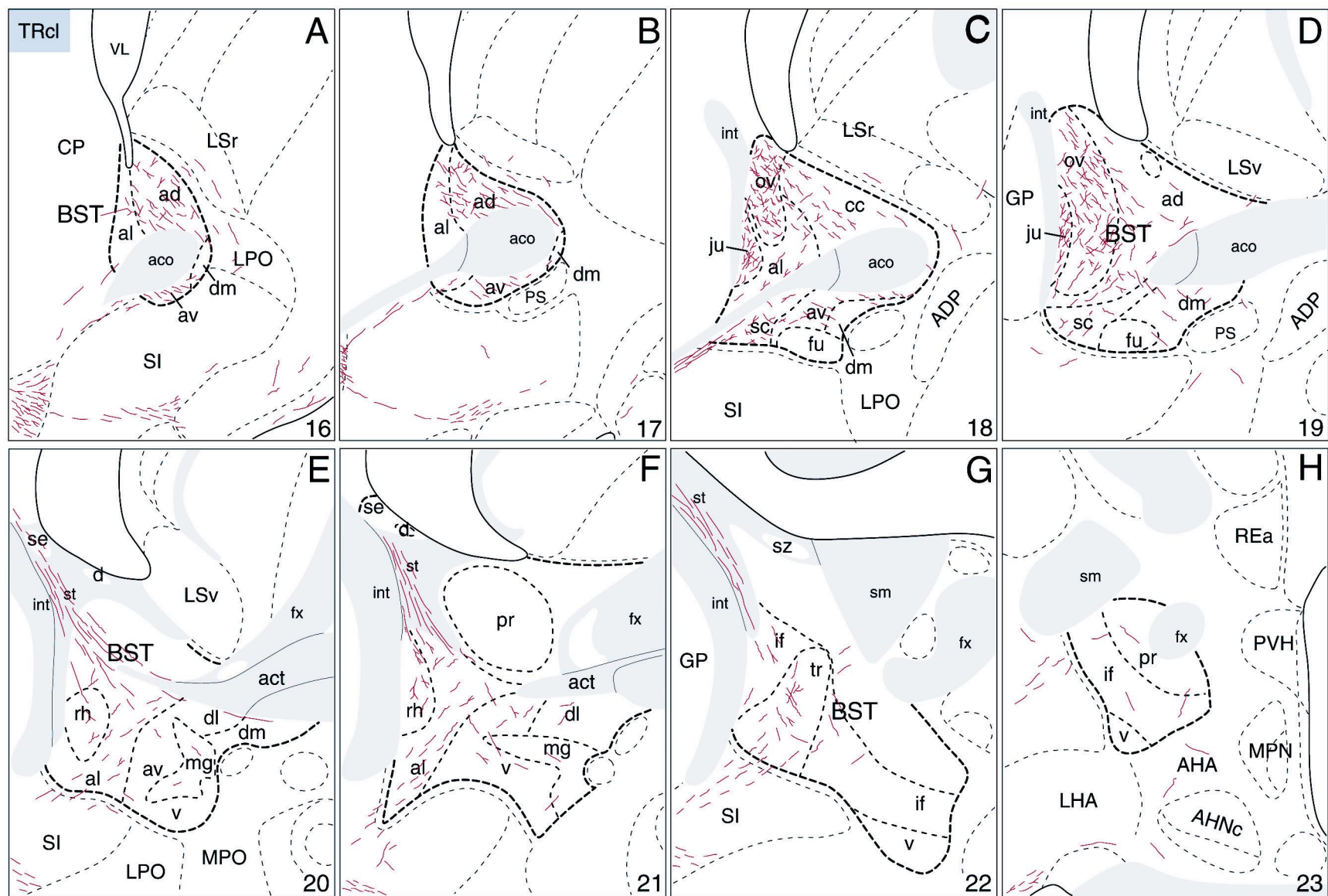


Fig. 22. Distribution of PHAL-labeled projections (red) from caudolateral regions of the postpiriform transition area to the BST. The results of experiment #59 are plotted as in Fig. 6.

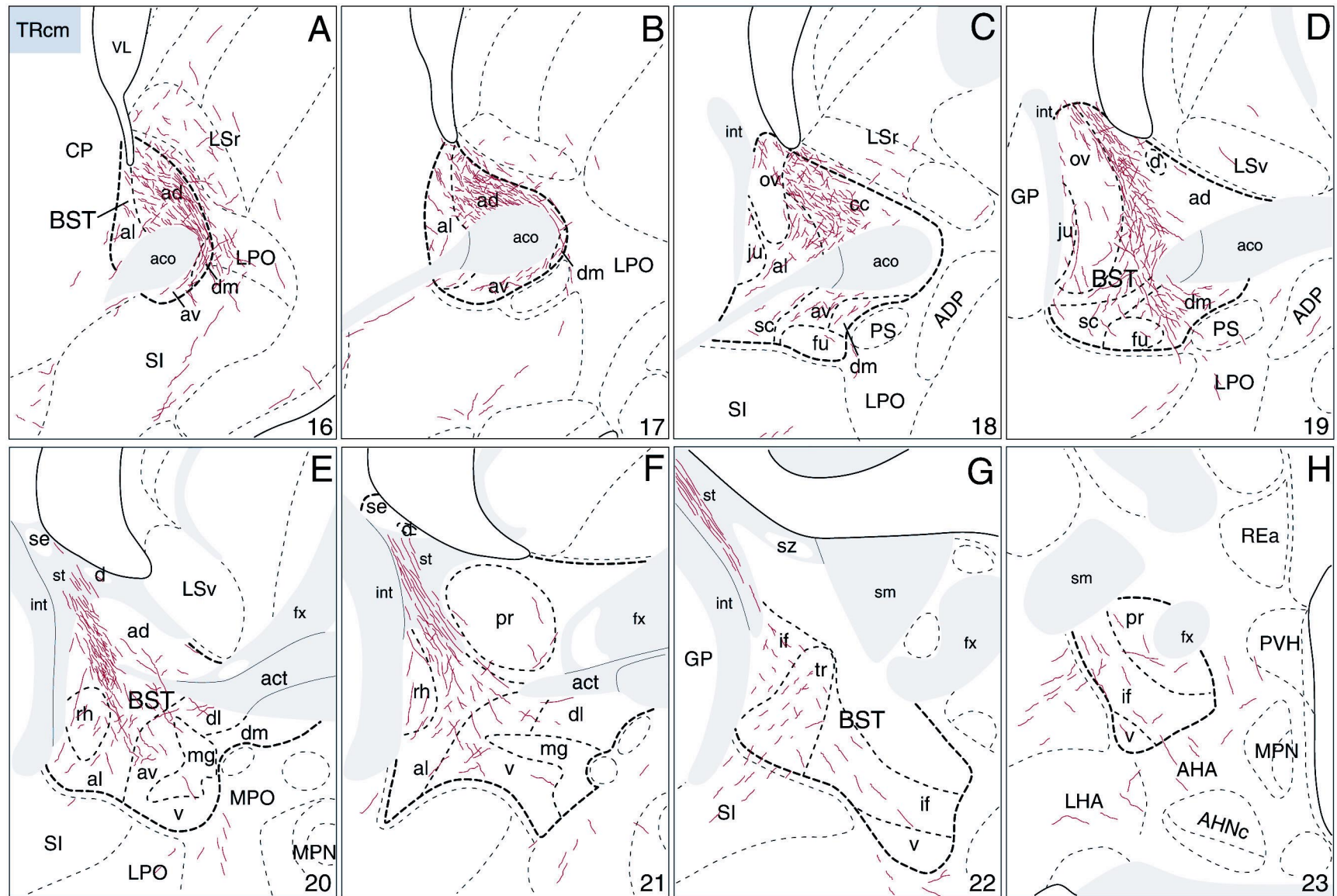


Fig. 23. Distribution of PHAL-labeled projections (red) from caudomedial regions of the postpiriform transition area to the BST. The results of experiment #77 are plotted as in Fig. 6.

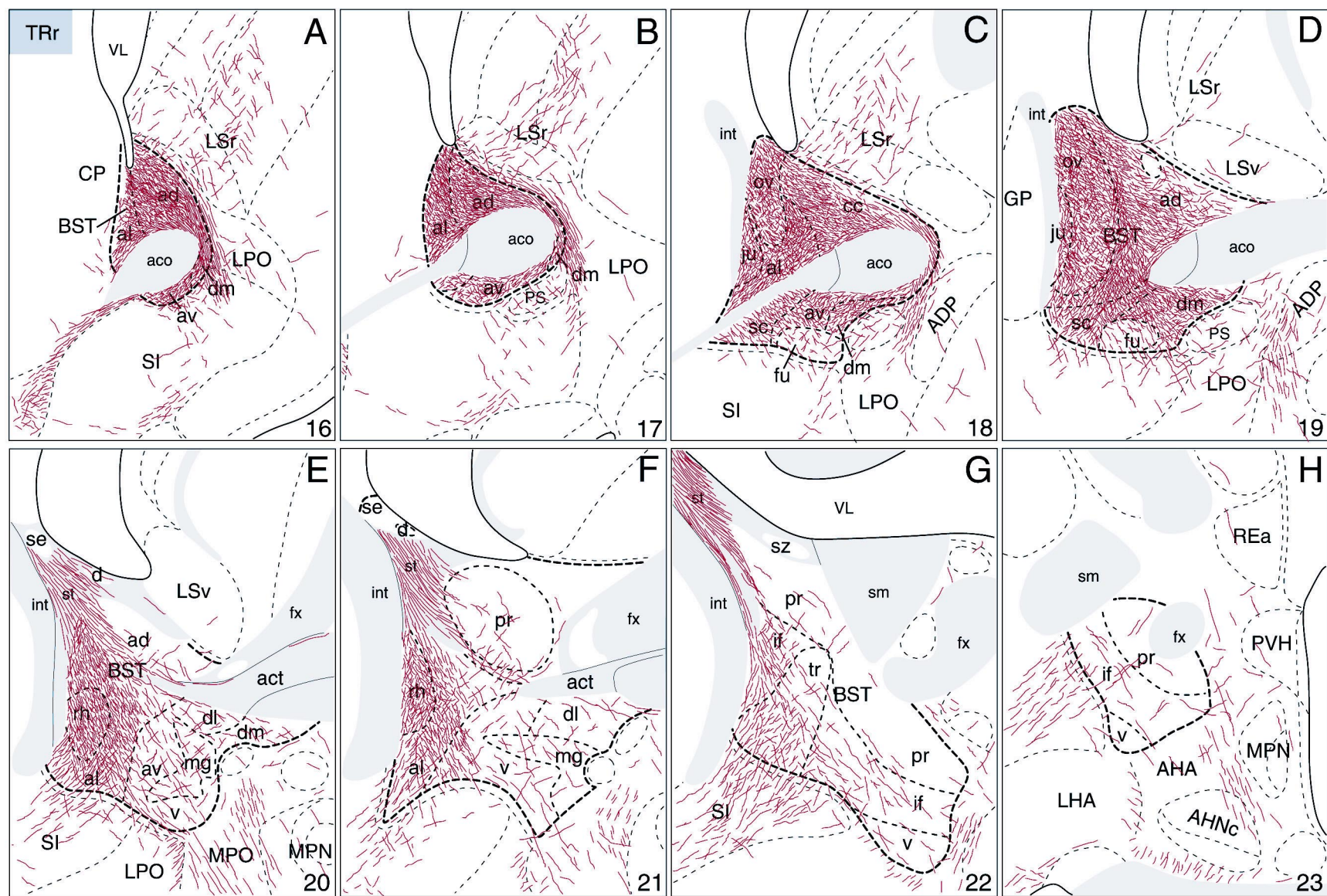


Fig. 24. Distribution of PHAL-labeled projections (red) from rostromedial regions of the postpiriform transition area to the BST. The results of experiment #76 are plotted as in Fig. 6.

s-of-passage in the transverse nucleus of experiment #76 (rostromedial) (Fig. 24G).

What we refer to as the postpiriform transition area [12] was first identified by Haug [39] as the ‘area interposed between area entorhinalis caudally, and the piriform cortex and the posterior pole of the amygdala rostrally,’ and was later called the amygdalopiriform transition area by De Olmos et al. [26]. Its pattern of inputs to the BST obviously does not resemble that of any of its cortical neighbors (Fig. 3). Our results, though more detailed, are in general agreement with those of two recent PHAL analyses. Shammah-Lagnado and Santiago [91] found topographically organized projections from medial and lateral regions of the postpiriform area to their lateral division of the BST, whereas McDonald et al. [60,61] reported projections to their lateral and juxtacapsular subdivisions of the BST. Clearly, more experimental work is required to understand fully the organization of projections from the postpiriform area.

4.3.6. From the posterior basomedial nucleus

As mentioned in the introduction to this Section, the posterior basomedial nucleus — along with the piriform–amygdalar area and posterolateral cortical nucleus to be considered next — belong to the group of main olfactory system-related amygdalar cell groups that project to the posterior division of the BST, along with the accessory olfactory system-related amygdalar cell groups (Fig. 3). We have already described the overall pattern of posterior basomedial projections, and the associated literature [75]. To illustrate posterior basomedial nucleus projections to the BST in detail we shall use experiment #28 (Fig. 17).

As shown in Fig. 25, most axons from the posterior basomedial nucleus to the BST travel through the stria terminalis in preference to the ventral route through the ansa peduncularis. Generally speaking, it would appear that a majority of axons from the posterior basomedial nucleus course through the precommissural bundle of the stria (see Section 6.2), which travels through the anterodorsal area of the BST and then arches ventrally and caudally around the rostral face of the anterior commissure before extending into the hypothalamus. Within the anterior division of the BST itself, the posterior basomedial nucleus generates dense terminal fields in the anterodorsal area and magnocellular nucleus (Fig. 25A–F), and much lighter terminal fields in the anteroventral area, dorsomedial nucleus, and subcommissural zone (Fig. 25A–F). Interestingly, there was also a rather clear terminal field in the boundary region between the rostral anterolateral area of the BST and the adjacent caudoputamen (Fig. 25A,B). In the posterior division of the BST, the posterior basomedial nucleus appears to provide a relatively light input to the transverse nucleus (Fig. 25G).

4.3.7. From the piriform–amygdalar area

The following description is based on a PHAL injection

that was centered in layers 2 and 3 of this area, which was originally identified by Crosby and Humphrey in 1941 [21]. There was minimal spread of the injection to immediately adjacent regions of the posterior basomedial nucleus (Fig. 17, experiment #POLC-3), which lies just deep to the piriform–amygdalar area (Fig. 1). We are unaware of earlier literature on projections from the piriform–amygdalar area to the BST, or anywhere else.

Curiously, the projection of the piriform–amygdalar area upon the BST (Fig. 26) is rather similar to that from the posteroventral part of the medial amygdalar nucleus (Figs. 3 and 13). Thus, a majority of projections from the piriform–amygdalar area travel through the stria terminalis to the BST, where major terminal fields are generated in the transverse and interfascicular nuclei (Fig. 26G–H). In the anterior division of the BST there is a dense terminal field in the caudal end of the anterodorsal area, and much lighter terminal fields in the rostral two-thirds of the anterodorsal area, dorsomedial nucleus, and rostral end of the anterolateral area (Fig. 26A–F). Because there is no other information available about the projections of the piriform–amygdalar area, it may be worth mentioning that in experiment #POLC-3 dense projections were also labeled to many regions of the amygdala including the medial and capsular parts of the central nucleus, the anterodorsal and posterodorsal parts of the medial nucleus, all parts of the basomedial and cortical nuclei, the lateral nucleus, the anterior area, and the postpiriform transition area. In the cortical mantle, dense projections to the infralimbic, dorsal and ventral agranular insular, perirhinal, piriform, and entorhinal areas were labeled, along with significant inputs to the dorsal endopiriform nucleus and ventral field CA1 of the hippocampus proper (also see [74]).

4.3.8. From the posterolateral cortical nucleus

Projections from this differentiation of the periamygdalar cortex have been dealt with elsewhere, along with the earlier literature [12]. For detailed illustration of its input to the BST, experiment #POCL-2 (Fig. 17) will be utilized. The injection site was centered in layer 3, and spread somewhat to involve adjacent regions of the posterior nucleus, which lies immediately deep to the posterolateral cortical nucleus (Fig. 1). As we shall see, the posterolateral cortical nucleus and the posterior nucleus establish quite distinct patterns of terminal fields within the BST (Fig. 3).

The overall pattern of projections from the posterolateral cortical nucleus to the BST (Fig. 27) resemble those already described from the posteroventral part of the medial amygdalar nucleus and the piriform–amygdalar area (Figs. 3, 13 and 26). Thus, most axons from the posterolateral cortical nucleus to the BST travel through the stria terminalis (Fig. 27G), and when they enter the posterior division they branch profusely and establish major terminal fields in the transverse and interfascicular

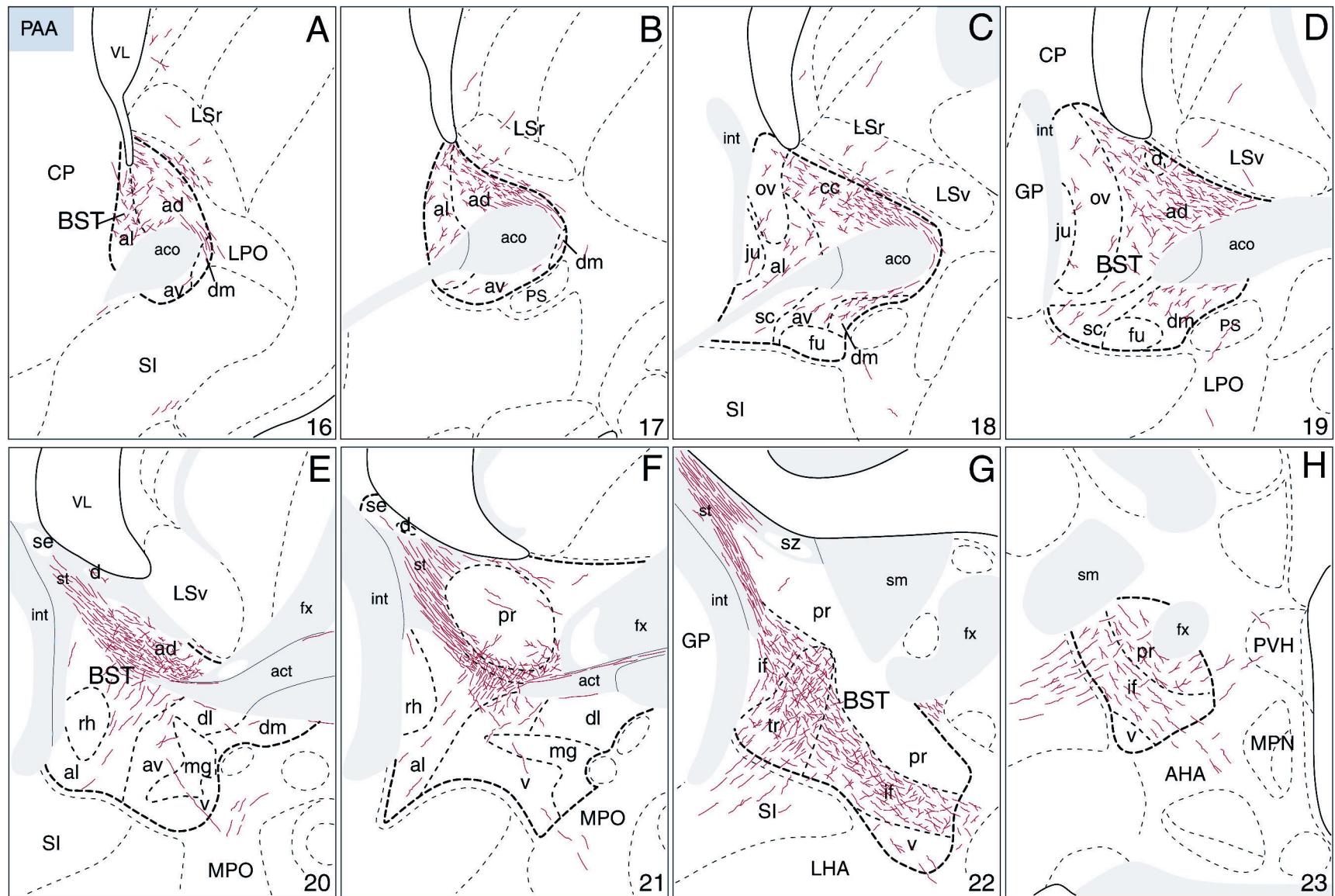


Fig. 26. Distribution of PHAL-labeled projections (red) from the piriform-amygdalar area to the BST. The results of experiment #POCL-3 are plotted as in Fig. 6.

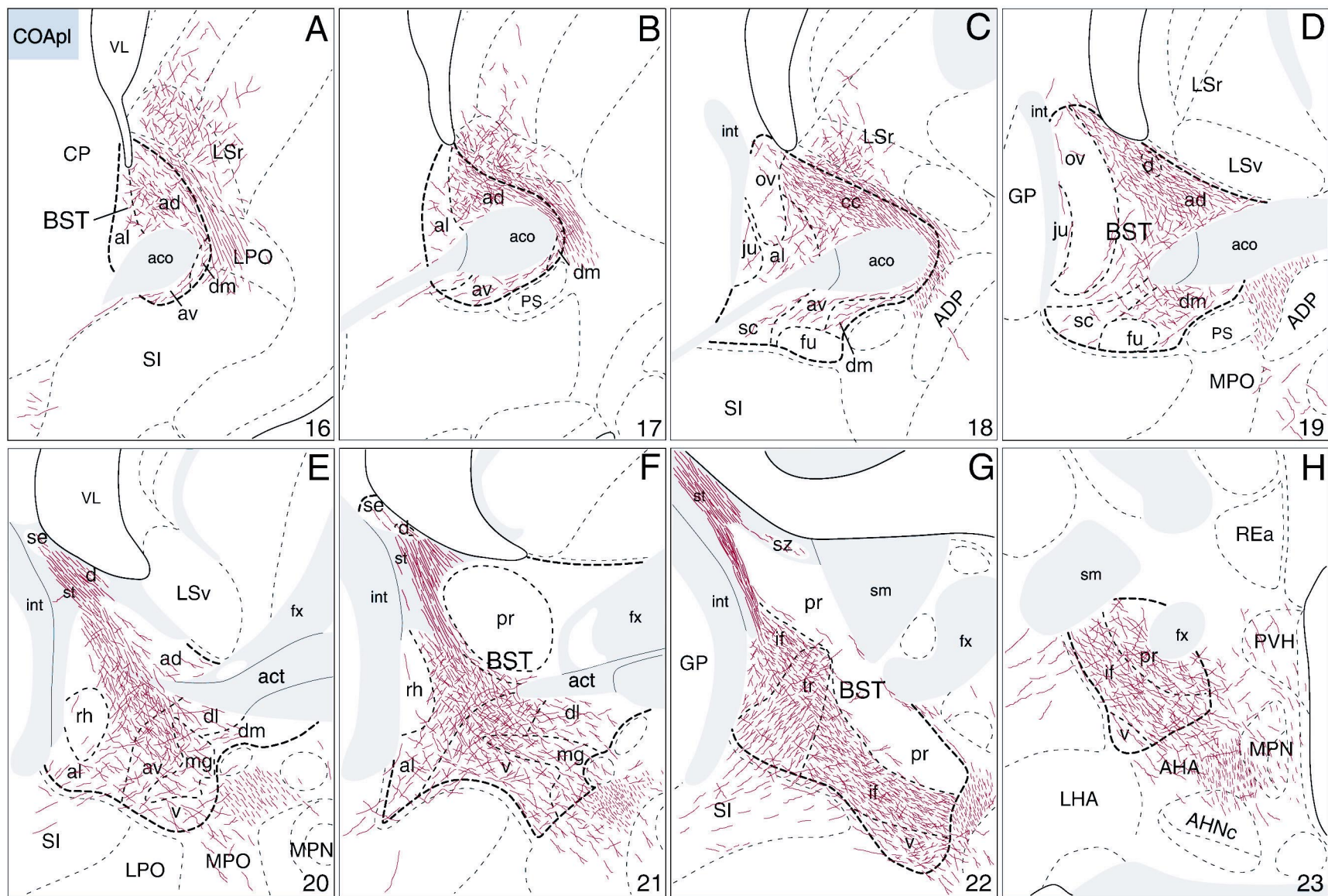


Fig. 27. Distribution of PHAL-labeled projections (red) from the posterolateral cortical nucleus to the BST. The results of experiment #POCL-2 are plotted as in Fig. 6.

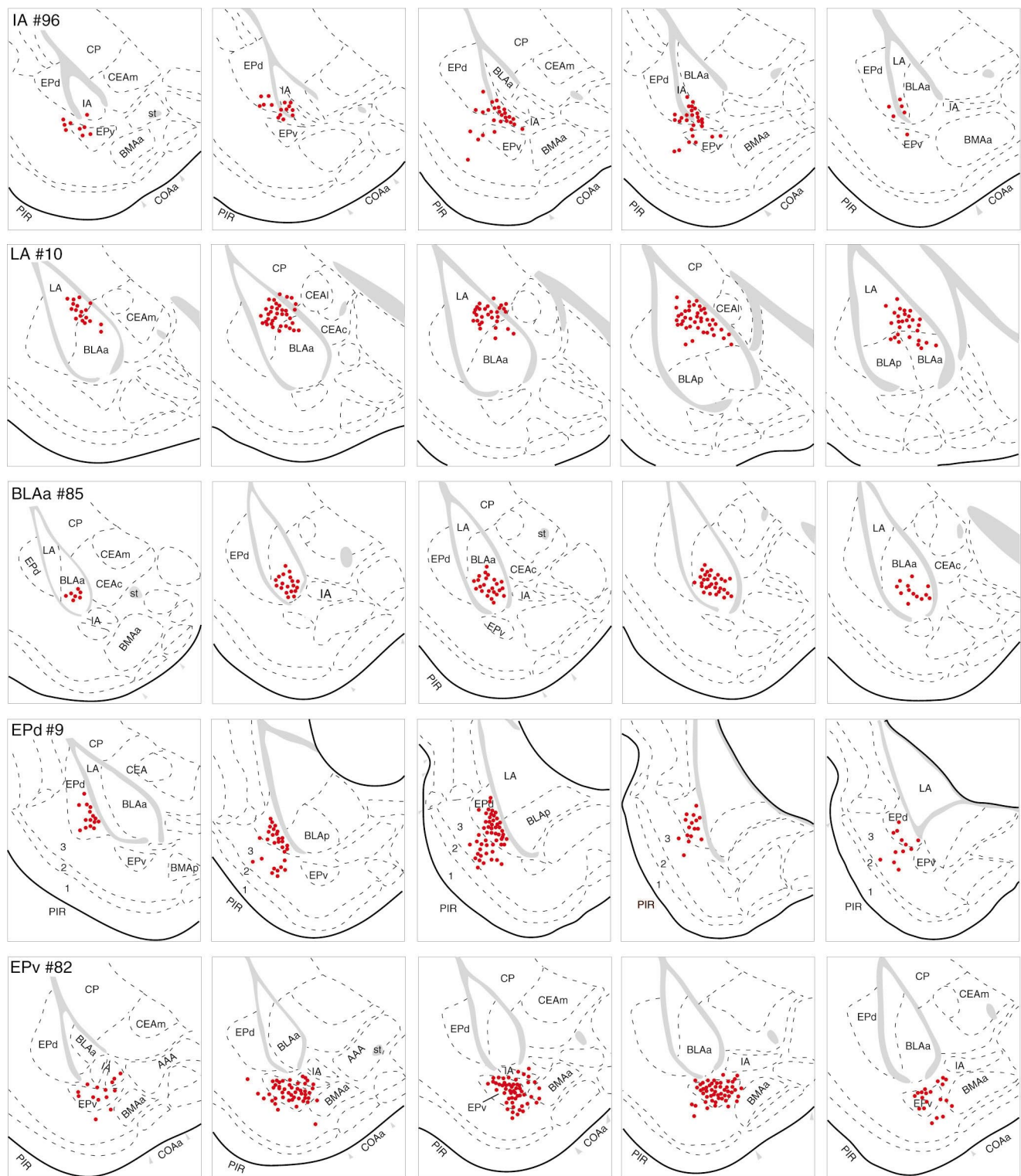


Fig. 28. PHAL injection sites involving the intercalated, anterior basolateral, lateral, dorsal endopiriform, and ventral endopiriform nuclei. Labeled neurons are plotted as described in Fig. 4.

nuclei, and in the caudal end of the principal nucleus (Fig. 27G,H). In addition, the dorsal nucleus receives a moderate input (Fig. 27D).

In the anterior division of the BST axons from the

posterolateral cortical nucleus branch substantially and generate many boutons in the anterodorsal area, caudal regions of the anteroventral area, and dorsomedial and ventral nuclei (Fig. 27A–F). Lighter inputs to the mag-

nocellular and dorsolateral nuclei are also found (Fig. 27E,F). Many labeled axons are observed in caudal regions of the anterolateral area, but they seem to be fibers-of-passage because they generate very few boutons (Fig. 27E,F).

4.3.9. From the intercalated nuclei

These enigmatic clusters of GABAergic [67,69] neurons, which have been described on the basis of Golgi material as a possible ‘ventral extension of the corpus striatum’ [62], are so small and irregular in rats that they are probably refractory to current methods of PHAL analysis. Nevertheless, it is worthwhile describing one experiment (#96, see Fig. 28) that labeled many neurons in one of the larger intercalated cell groups, along with many neurons in adjacent regions of the lateral amygdalar nucleus, endopiriform nucleus, and piriform area. The reason for mentioning this experiment is that no significant projections to the BST were labeled, although many other pathways in the brain were labeled clearly. This is a very fortunate injection because the areas labeled around the intercalated nucleus in this experiment also do not, by and large, appear to innervate the BST even moderately densely (see Section 4.4). It should also be mentioned that Weller and Smith [115] did not observe retrograde labeling of the intercalated nuclei after HRP injections in the rat BST.

4.4. Projections from the frontotemporal association system

There is no evidence in the literature, or from our own PHAL collection, for significant projections to the BST (or hypothalamus) from the lateral amygdalar nucleus (e.g., experiment #10 in Fig. 28) or from the anterior basolateral (magnocellular basal) nucleus (e.g., experiment #85 in Fig. 28).

5. Projections from other cerebral regions to BST

We have just seen that not all cell groups associated with the amygdala project to the BST, and conversely it should be borne in mind that other parts of the cerebral hemispheres also project to the BST. Because we have very useful PHAL injections in several of these extra-amygdalar sites, their projections to the BST will be considered briefly for the sake of completeness.

5.1. From the endopiriform nucleus

This region is often considered a ventral expansion of the claustrum for the overlying piriform area. One PHAL experiment in our collection (#9 in Fig. 28) was centered in the relatively large dorsal part of the endopiriform nucleus, and spread to include a substantial population of

neurons in layer 3 of the adjacent piriform area. There was no significant labeling of the BST in this experiment, which simply confirms the negative results of other workers [8,51,89].

On the other hand, a very fortunate PHAL injection (#82 in Fig. 28) filled most of the ventral endopiriform nucleus [52] at the level of the anterior basolateral nucleus, with minimal spread to two regions not thought to project to the BST (the piriform area and intercalated nuclei), and a few labeled neurons in the anterior basomedial nucleus. From this injection site a relatively small group of labeled axons courses ventrally through the ansa peduncularis to reach the posterior division of the BST, along with an even much smaller number of axons in the stria terminalis (Fig. 29). In the posterior division of the BST light terminal fields were observed in the transverse nucleus and caudal tip of the interfascicular nucleus (Fig. 29G,H). Many of the axons extend into the anterior division of the BST, where light terminal fields were observed in the anterodorsal, anteroventral, and anterolateral areas, and in the magnocellular nucleus (Fig. 29A–F). This pattern is quite distinct from that generated by the anterior basomedial nucleus (Fig. 3). We are unaware of any other literature dealing critically with a projection from the ventral endopiriform nucleus to the BST. Overall, it seems clear that the piriform area and subjacent endopiriform nucleus generate a rather insubstantial projection to the BST.

5.2. From the ventral subiculum

The ventral subiculum is a component of the hippocampal formation that lies immediately adjacent to the posterior amygdalar nucleus (amygdalo–hippocampal transition area) and is the major contributor to the medial corticohypothalamic tract, a component of the fornix system that projects to many of the same regions as the stria terminalis (see [15,102]). We have analyzed the overall projections from the ventral end of the subiculum, and the relevant older literature, in earlier publications [15,74], and here will simply illustrate in greater detail inputs to the BST from the prototypical experiment (#SUB16 in Fig. 30) in that paper.

Many axons from the ventral subiculum travel through the distal tip of the fimbria to enter caudal regions of the septum, and many of these fibers continue ventrally to innervate the BST (Figs. 3 and 31). In the anterior division of the BST, the major terminal field is in the anterodorsal area (Fig. 31A–D), although the anteroventral area (including the dorsomedial, magnocellular, and ventral nuclei) also receives a light input (Fig. 31A–F). The lateral group of structures in the anterior division of the BST is virtually free of PHAL labeling (Fig. 31A–F). In the posterior division of the BST, numerous labeled axons with abundant terminal boutons and boutons-of-passage fill the transverse and interfascicular nuclei, and the caudal end of the principal nucleus (Fig. 31G,H). It is obvious

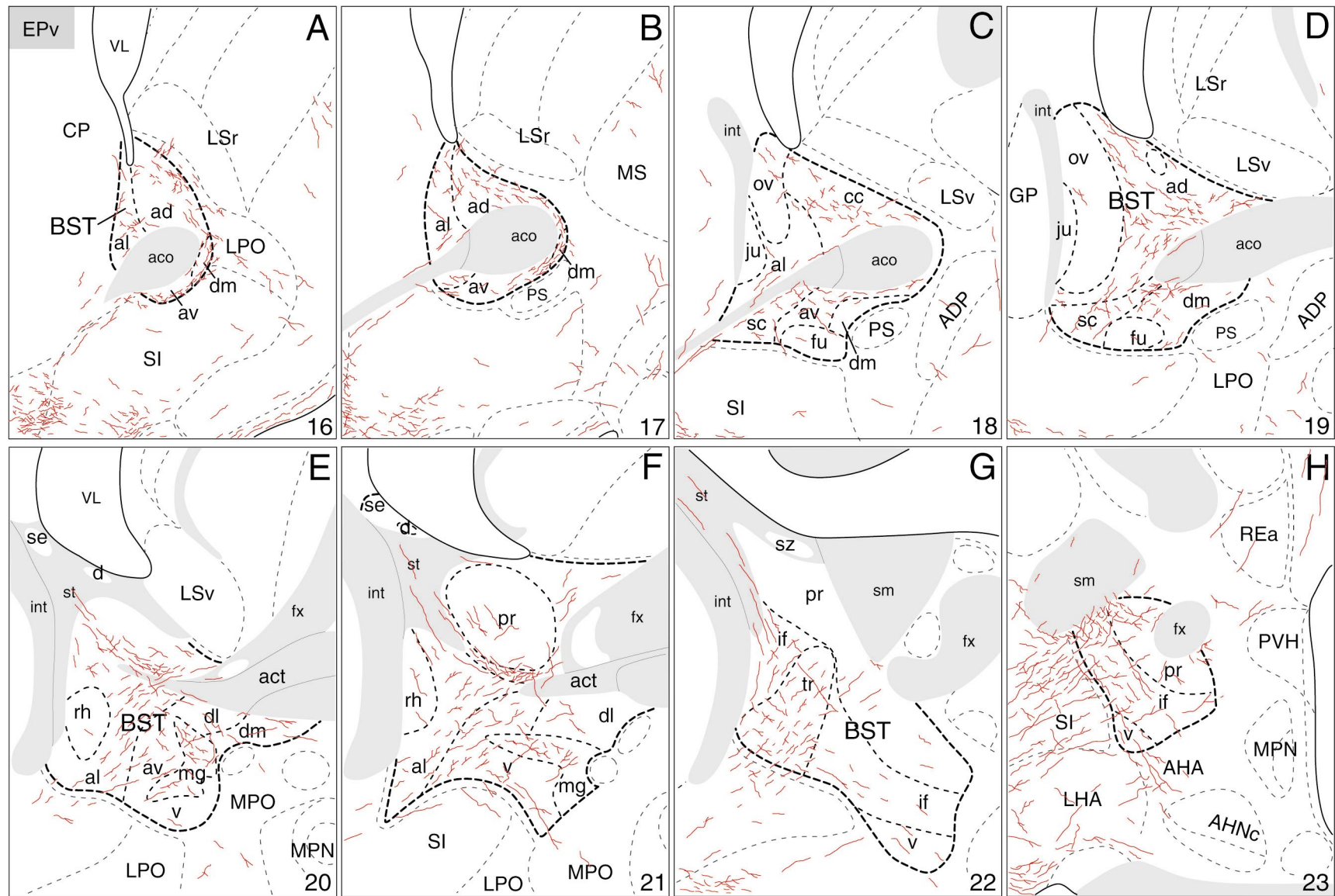


Fig. 29. Distribution of PHAL-labeled projections (red) from the ventral endopiriform nucleus to the BST. The results of experiment #82 are plotted as in Fig. 6.

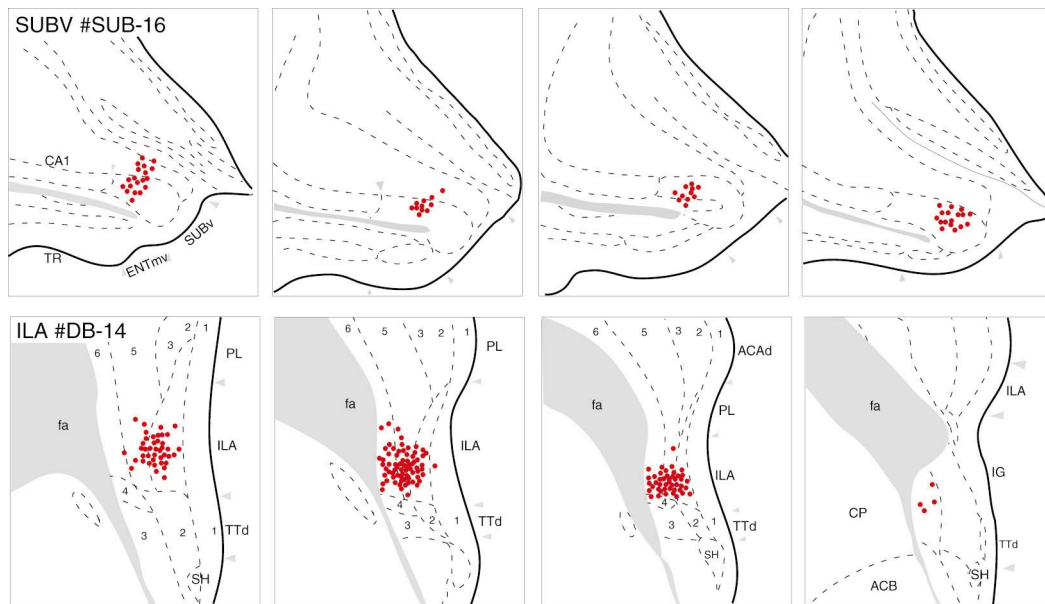


Fig. 30. PHAL injection sites involving the ventral subiculum and infralimbic area of the medial prefrontal cortex. Labeled neurons are plotted as described in Fig. 4.

from Fig. 3 that the pattern of inputs to the BST from the ventral subiculum is complementary to that from the posterior nucleus of the amygdala.

Although considerably more detailed, our results are in general agreement with those of Cullinan et al. [22] and of Kishi et al. [49]. However, there are reasons to believe that projections from this region of the hippocampal formation show great topographical differentiation (see [74]), and it seems likely that this holds true for its input to the BST. Clearly, more experimental work is needed on this important problem.

5.3. From the infralimbic area

This part of the prefrontal region and the ventral subiculum are probably the two most important extra-amygdalar sources of cortical input to the BST, and it is thus of considerable interest that the ventral subiculum projects substantially to the infralimbic area (see [65,104]). We have reanalyzed in detail the organization of projections from the infralimbic area to the BST in PHAL experiments from our laboratory used for a more general description of overall infralimbic output [11]. A prototypical experiment where the injection site was confined entirely to the infralimbic area, and labeled neurons in layers 2–6 (experiment #DB-14 in Fig. 30), will be used to illustrate inputs to the BST (Fig. 32).

The most dense BST terminal fields labeled in experiment #DB-14 were in the anterior division. Unlike most amygdalar cell groups and the ventral subiculum, the infralimbic area provides a dense input to the anteroventral rather than anterodorsal area. In the anteroventral area, the most obvious terminal fields were in caudal regions of the

anteroventral area itself, and in the dorsomedial, dorsolateral, magnocellular, and ventral nuclei (Fig. 32C–F). In contrast, the posterior division of the BST is only lightly innervated, with most of these fibers and boutons found in the transverse and interfascicular nuclei (Fig. 32G,H).

Although more detailed, these observations are in general agreement with other work. Hurley et al. [43] reported that the infralimbic area targets mainly the ‘lateral and ventrolateral’ portions of the BST. McDonald et al. [61] and Vertes and Todorova [114] agree that the infralimbic area projects mainly to the anteroventral area of the BST, although both groups also reported that the infralimbic area projects to the ‘posterolateral division of the medial BST’, which may correspond to our interfascicular and transverse nuclei. Takagishi and Chiba simply reported inputs throughout the BST [109].

6. Discussion

The results presented above indicate that amygdalar cell groups associated with particular functional systems project upon the BST in highly organized ways (Fig. 3). Overall, the autonomic part of the amygdala innervates the anterior BST; accessory olfactory parts of the amygdala innervate the posterior BST and medial group of the anterior BST; and some parts of the main olfactory amygdala project to the BST like the autonomic part, whereas other parts of the main olfactory amygdala project to the BST like the accessory olfactory part. The real significance of this projection pattern can only be appreciated when the output of each part of the BST is known, which is not yet the case. Nevertheless, it is

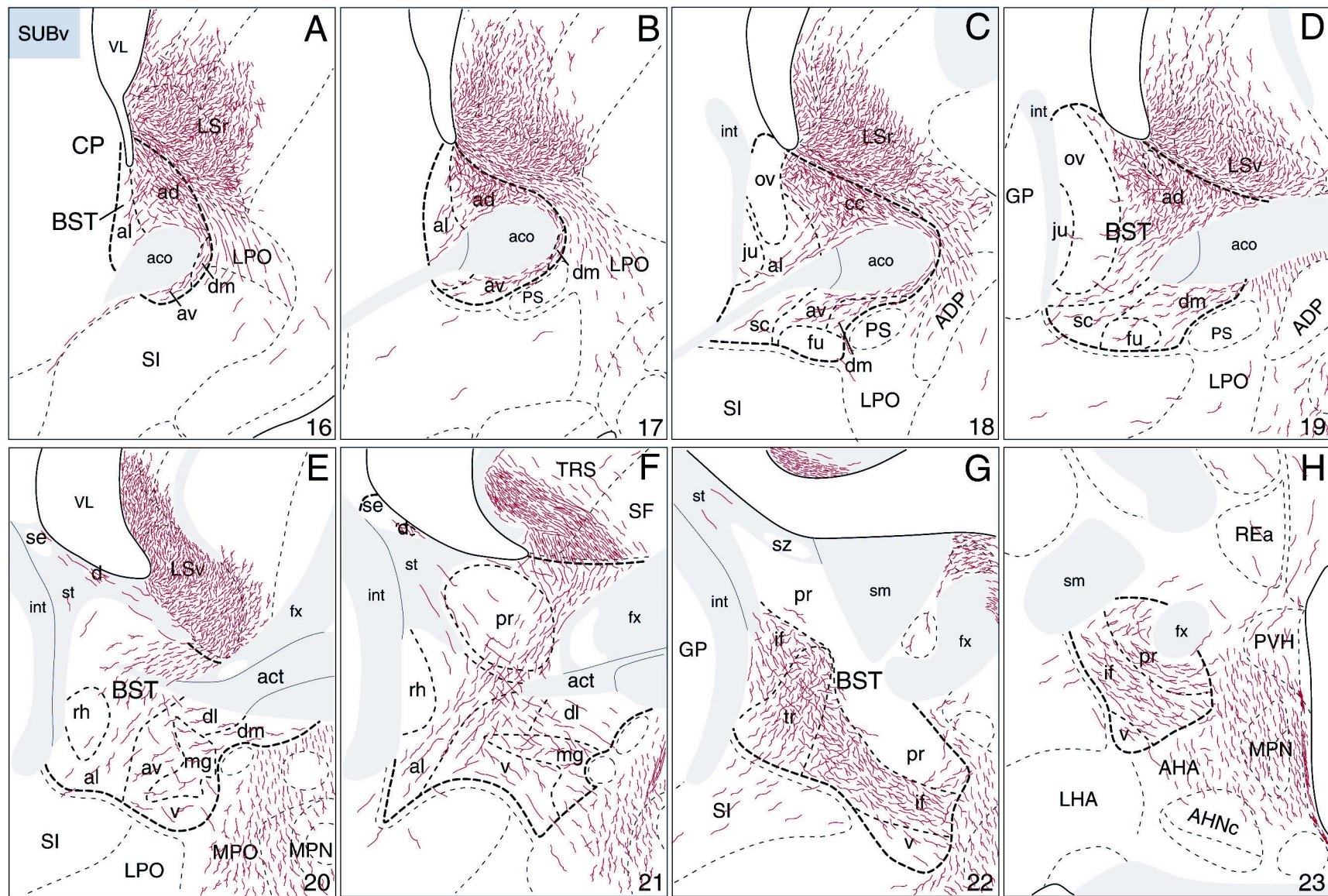


Fig. 31. Distribution of PHAL-labeled projections (red) from the ventral subiculum to the BST. The results of experiment #SUBv-16 are plotted as in Fig. 6.

fundamentally important to establish precisely how each of these BST cell groups is innervated, whether or not their outputs are known at this time.

6.1. Overview of amygdalar terminal fields in the BST (Fig. 3)

The central nucleus is a well-recognized component of the cerebral autonomic control system, and together its various parts innervate most of the anterior division of the BST — the only clear exceptions are the juxtacapsular, dorsolateral, and ventral nuclei. In contrast, the medial nucleus, which is a component of the pheromonal or accessory olfactory system innervates all parts of the posterior division of the BST, as well as all parts of the medial group of the anterior division. As a matter of fact, all three amygdalar parts of the pheromonal system share this dual projection to the posterior division and medial (but not lateral) group of the anterior division. However, there is an interesting topography within the broader pattern. The posterior nucleus and the posterodorsal medial nucleus, which is sexually dimorphic [92,95], project to the sexually dimorphic principal nucleus (and another tiny cell group, the dorsal nucleus); whereas the other parts of the medial nucleus and the posteromedial cortical nucleus project most densely to the transverse and interfascicular nuclei. Curiously, a component of the pheromonal system, the posteromedial cortical nucleus, was the only part of the amygdala that we identified as generating a substantial projection through the anterior commissure to the contralateral BST and amygdala. Finally, we should mention that projections from amygdalar components of the autonomic and pheromonal systems are differentially distributed within the anterodorsal area of the BST. Thus, projections from the central nucleus are essentially restricted to the rostral end and central core, whereas components of the accessory olfactory system preferentially innervate medial and caudal regions.

Turning now to components of the amygdala that are most closely associated with the main olfactory system, they can be divided into two groups based on the pattern of their inputs to the BST. The projections of one group is similar to that from the central nucleus insofar as the posterior division of the BST is largely avoided, and the lateral group of the anterior division is more heavily innervated than the medial group. This first group of amygdalar components includes the anterior area (striatal), the anterior cortical nucleus and its associated claustral/subplate mate the anterior basomedial nucleus, and the postpiriform transition area and its associated claustral/subplate mate the posterior basolateral nucleus. Typically, the cortical components of this group (the anterior cortical nucleus and caudal postpiriform transition area) project less heavily to the BST than the claustral/subplate and striatal components — except for the rostral postpiriform area, which projects densely to the BST. Within the lateral

group of the anterior BST, the subcommissural zone, rhomboid nucleus, and caudal regions of the anterolateral area receive the heaviest inputs from these parts of the amygdala. In contrast, the fusiform and oval nuclei, which receive dense inputs from the central amygdalar nucleus, are only lightly innervated by the main olfactory group of amygdalar parts under consideration here — except for the rostral postpiriform area, which innervates densely the oval nucleus. Notably, the rostral end of the anterolateral area and the juxtacapsular nucleus, which are avoided by inputs from the central amygdalar nucleus, receive dense projections specifically from the postpiriform area and its associated deep region, the posterior basolateral nucleus. For the sake of completeness, it should be mentioned that the lateral edge of the transverse nucleus and the interfascicular nucleus (both of the posterior BST division) may receive a light input from this first group of the main olfactory system.

The second group of amygdalar components related closely to the main olfactory system resembles more in its BST projection the medial amygdalar nucleus (and other components of the accessory olfactory system) than the central amygdalar nucleus. This second group includes the piriform–amygdalar area and its claustral/subplate mate the posterior basomedial nucleus, along with the posterolateral cortical nucleus, and at least part of the posterior nucleus, which it seems to share with the posteromedial cortical nucleus. Basically it projects to the posterior division of the BST and to the medial but not lateral group of the anterior division. We have included the posterior basomedial nucleus in this second group because although it does not project heavily to the posterior division of the BST, it does project massively to the ventromedial hypothalamic nucleus [75], like the nuclei of the posterior division of the BST (our unpublished observations with PHAL).

It should also be noted that all components of the amygdala closely associated with the main olfactory system project to the medial group of the anterior BST division. The anterodorsal and anteroventral areas, and the dorsomedial nucleus, receive the heaviest inputs from most of these parts of the amygdala, whereas the dorsolateral and ventral nuclei are innervated only by the anterior basomedial and posterolateral cortical nuclei, and the magnocellular nucleus receives a restricted, dense input only from the posterior basomedial nucleus. Perhaps not surprisingly, the differentiated anterodorsal area receives topographically organized inputs from the main olfactory group of amygdalar cell groups. Thus, the piriform–amygdalar area, posterior basomedial nucleus, and posterolateral cortical nucleus target more medial and caudal regions of the anterodorsal area of the BST (like the accessory olfactory system), whereas the other main olfactory-associated amygdalar cell groups preferentially innervate rostral and central core regions of the anterodorsal area (like the central nucleus of the amygdala).

Finally, the lateral and anterior basolateral amygdalar nuclei, which we have included in the frontotemporal association corticostriatal system, do not appear to innervate directly the BST to any appreciable extent.

6.2. Overview of projection pathways from amygdala to the BST

Axons from the various cell groups associated with the amygdala project in differentiated ways through the stria terminalis and ansa peduncularis to the BST and other subcortical sites (Fig. 33). Generally speaking, the great majority of axons arising from amygdalar cell groups that heavily innervate the posterior BST division (Fig. 3) course through the stria terminalis in preference to the ventral, ansa peduncularis route. In contrast, most axons from the anterior amygdalar area course through the ventral pathway, whereas the rest of the amygdalar cell groups utilize more or less equivalently both the stria terminalis and ansa peduncularis. As a corollary of this observation, the substantia innominata receives most of its amygdalar inputs from cell groups that use the ventral, ansa peduncularis pathway (see Figs. 6–9, 11, 13–16, 18–27). We should emphasize that it is not possible in our PHAL material to differentiate within the BST between terminal fields established by fibers in the stria terminalis and ansa peduncularis.

Of equal interest, axons from different components of the amygdala occupy distinct positions as they course through the stria terminalis. The details of this organization are so complex that they can only be appreciated, described, and examined adequately when viewed in graphic form (Fig. 34). However, at a very gross level of analysis, it would seem that when one examines cross sections of the body of the stria terminalis (along the dorsal, more or less horizontal, segment of its course between the amygdala and BST, Fig. 34A) axons arising from amygdalar cell groups that innervate heavily the posterior BST division (Fig. 3) are concentrated in roughly the dorsal half of the stria terminalis (dorsal to the longitudinal axis of its cross-sectional profile), whereas amygdalar cell groups that innervate densely the lateral group of the anterior BST division (Fig. 3) are concentrated in roughly the ventral half of the stria terminalis. Furthermore, axons traveling in more dorsal regions of this segment of the stria terminalis arise from the medial nucleus and other components of the accessory olfactory system and relatively medial components of the main olfactory system (Fig. 34B). In contrast, axons traveling in more ventral regions of this segment of the stria terminalis arise from the central nucleus and relatively lateral components of the main olfactory system (Fig. 34B). It is important to bear in mind for the following discussion that all amygdalar regions contributing to the stria terminalis innervate the medial group of the anterior BST division (Fig. 3).

In his classical account Johnston [45] identified five

seemingly discrete bundles within the stria terminalis, and described how they separate and become more distinct at the level of what we now recognize as the BST (Fig. 35). His bundles included: commissural, hypothalamic, infracommissural, supracommissural (parolfactory or septal, and hypothalamic parts), and stria medullaris. More contemporary authors have failed to recognize stria terminalis fibers entering the stria medullaris, and have tended to simplify the problem by recognizing just three bundles: precommissural (supracommissural), commissural, and postcommissural (ventral) (e.g., [40,54]). However, in the most recent systematic analysis (almost 30 years ago) de Olmos [25,28] recognized in the stria terminalis a ventral bundle that formed postcommissural fibers at the level of the BST, a dorsal bundle that formed both supracommissural (precommissural) and retrocommissural (postcommissural) fibers at the level of the BST, and a commissural bundle embedded in the middle of the ventral bundle. The supra- or precommissural component was said to innervate the anterior BST, lateral septal nucleus, and nucleus accumbens; the olfactory tubercle, anterior olfactory nucleus, and accessory olfactory bulb; and the 'medial preoptic–anterior hypothalamic junction area,' capsule of the ventromedial hypothalamic nucleus, and premammillary area; whereas in contrast, the postcommissural component of the stria terminalis was said to innervate the posterior BST, medial preoptic–anterior hypothalamic junction area, core of the ventromedial nucleus, and premammillary area.

It is not our intention here to provide an exhaustive analysis of exactly how amygdalar contributions to the stria terminalis distribute as they enter, innervate, and then leave the BST. However, it is worth making several general observations. First, it is easy to divide axons from the amygdala into two major bundles — precommissural and postcommissural — as they course through the BST itself, on the same side of the brain (Fig. 33). Clear subdivisions of these two pathways within the BST would be very difficult to establish without special stains (for example, the presence of a particular neuropeptide expressed by a restricted subset of amygdalar neurons). Second, the idea mentioned in the previous paragraph that distinct bundles can be identified within the dorsal stria terminalis itself is not substantiated by our results, and such bundles or fascicles are certainly not visible in normal histological material, from the rat at least. As shown in Fig. 33, all amygdalar cell groups that send axons into the stria terminalis contribute to the precommissural pathway and amygdalar axons that generate the postcommissural pathway to the posterior BST division (Figs. 3 and 33) tend to course through dorsal regions of the stria terminalis (Fig. 34A). Basically, our results suggest that axons from the amygdala in the stria terminalis do not separate or branch into pre- and postcommissural components until they begin entering the caudal end of the body of the BST (e.g., levels 20–23 in Fig. 6). And third, there are two

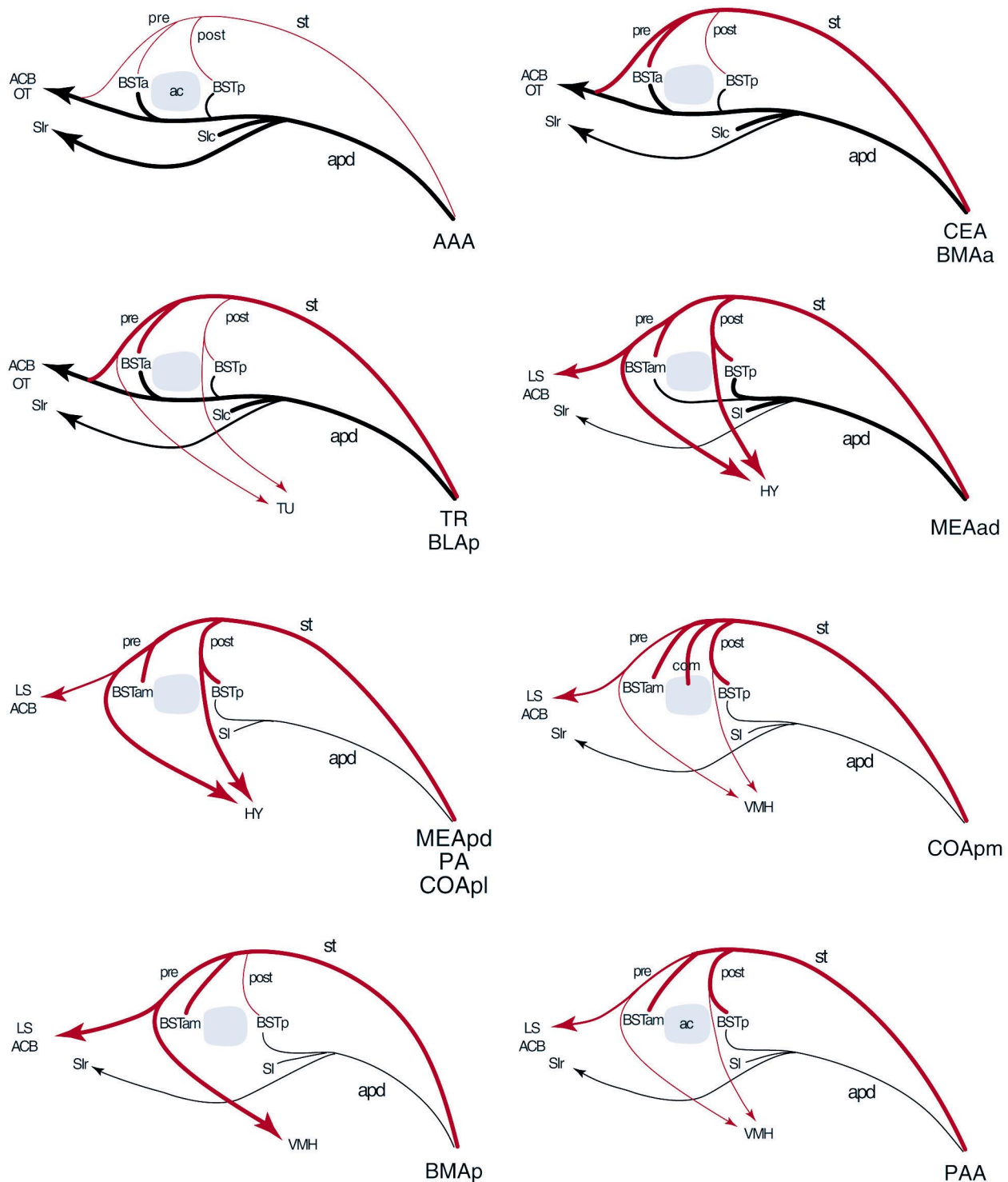
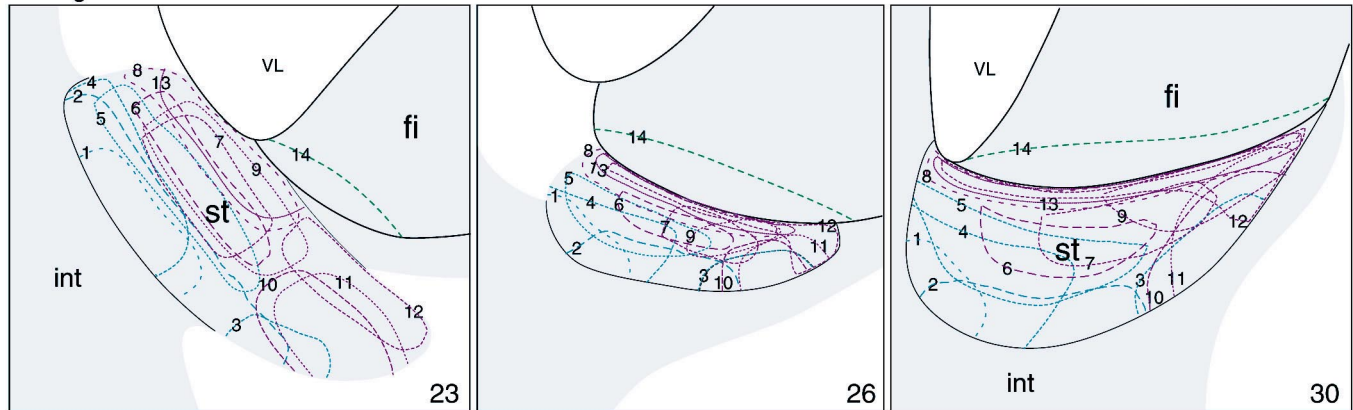


Fig. 33. Summary of how various amygdalar cell groups use the stria terminalis (dorsal, in red) and ansa peduncularis (ventral, in black) routes to innervate the BST, as well as adjacent regions of the basal ganglia/cerebral nuclei, and the hypothalamus. The schematic diagrams are based on an approximate sagittal projection, and relative strength of projections is indicated qualitatively by line thickness. Note that, broadly speaking, the stria terminalis (st) splits into precommissural (pre), commissural (com), and postcommissural (post) components as it enters and passes through the BST. The organization of these pathways is discussed in the text.

A. Organization of the stria terminalis



Sources of fibers: 1. CEAm, 2. BMAa, 3. COAa, 4. BLAp, 5. TR, 6. BMAp, 7. PAA, 8. COApl, 9. COApm, 10. MEApd, 11. MEApv, 12. MEApd, 13. PA, 14. SUBv (in fimbria)

B. Amygdala inputs to stria terminalis

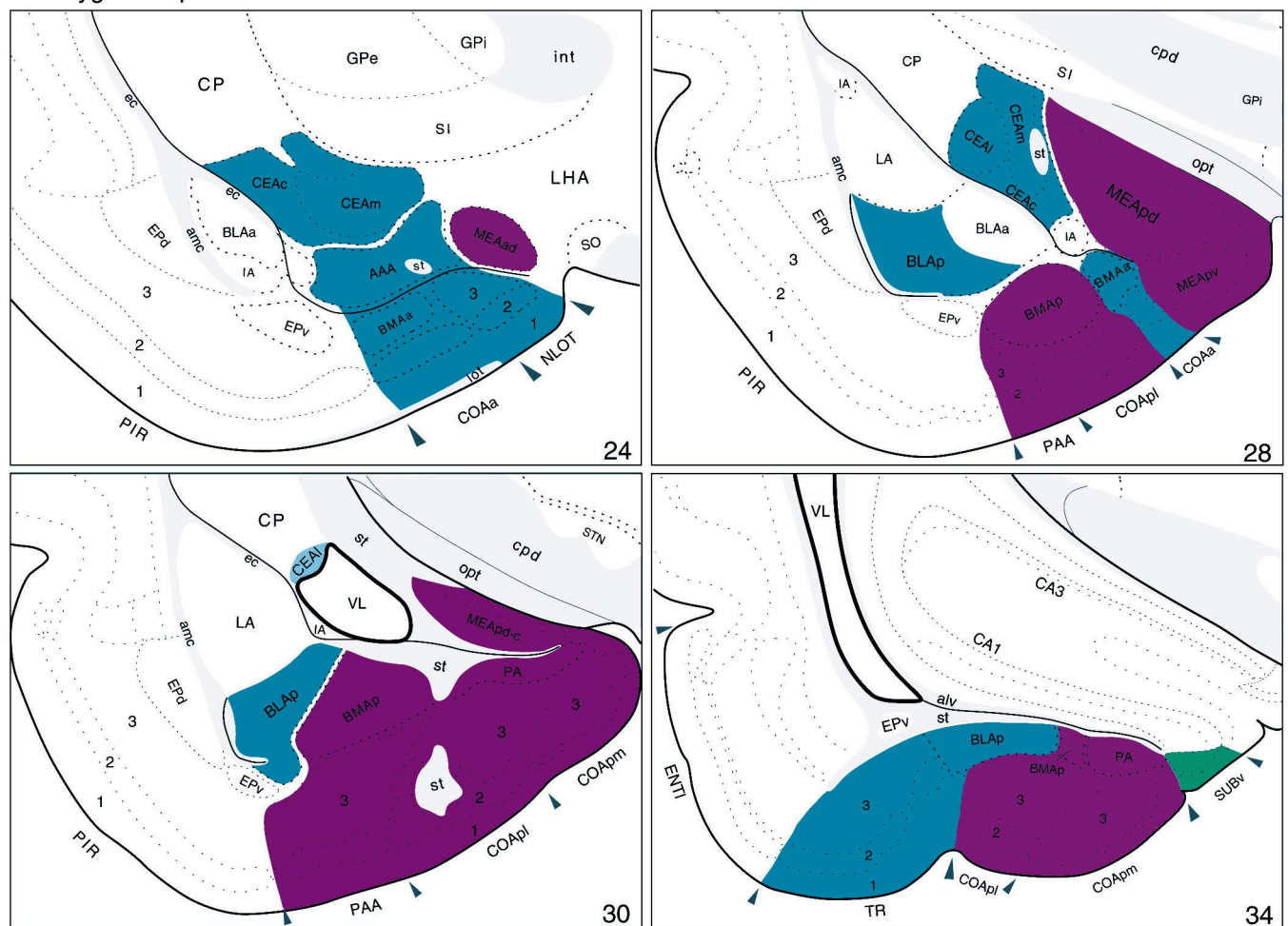


Fig. 34. Spatial organization of amygdalar projections through the stria terminalis to the BST. The rostralateral region indicated in blue (B) tends to send its fibers through relatively ventral regions of the stria terminalis (A) to the anterior BST division. Its major components are the central nucleus, and a number of amygdalar regions closely associated with the main olfactory system. In contrast, the more caudomedial region indicated in red (B) tends to send its fibers through relatively dorsal regions of the stria terminalis (A) to the posterior BST division and to the medial group of the anterior BST division (also see Figs. 1, 3 and 33). Its major components are the amygdalar members of the accessory olfactory system, along with three regions of the amygdala closely associated with the main olfactory system. (A) Three transverse cross sections through the left stria terminalis at atlas [100] levels 23, 26 and 30; to show where bundles of labeled axons are found after PHAL injections in various regions of the amygdala (dashed outlines indicated by numbers). (B) Rostrocaudally arranged atlas templates of the left rat amygdala, as in Fig. 1. For comparison, the projection path of the ventral subiculum (green) is shown in A (number 14). Note that projections from the amygdala descend through the stria terminalis, whereas those from the adjacent hippocampal formation descend through the fornix system (the alveus and then fimbria). Descending projections from the endopiriform nucleus tend to course through the ansa peduncularis/medial forebrain bundle, whereas those from the dorsally adjacent temporal cortex course through the internal capsule (lateral forebrain bundle).

obvious exceptions to the suggestion mentioned in the previous paragraph that fibers in the precommissural bundle innervate the capsule of the ventromedial hypothalamic nucleus, whereas the postcommissural bundle innervates the core of the nucleus. The posterior basomedial nucleus projects massively through the precommissural bundle (Fig. 33) to the core of the ventromedial nucleus [75]; and the anterodorsal and posterodorsal parts of the medial nucleus innervate the shell of the ventromedial nucleus [14] apparently via both the pre- and postcommissural bundles (Fig. 33).

The only amygdalar contribution to the commissural bundle that we could identify was the posteromedial cortical nucleus (Figs. 16 and 33). However, we did not have PHAL injections in the nucleus of the lateral olfactory tract, and there is clear evidence that it projects massively to the other side of the brain by way of the stria terminalis and anterior commissure (see [56]). It should also be noted that commissural projections through the anterior commissure have been documented from the anterior olfactory nucleus, anterior regions of the piriform area, and lateral entorhinal area (see [56]).

6.3. Total cerebral hemisphere input to the BST

Because of its very name, it is easy to assume that there is an exclusive relationship between the BST and the amygdala. However, the time may have come to question this assumption. In the first place, major parts of the amygdala — including the lateral and the anterior basola-

teral (magnocellular basal) nuclei do not project directly to the BST at all. Regions of the amygdala that do innervate the BST directly seem to be most closely associated with the autonomic and olfactory systems. Second, it is important not to forget that there are two major direct routes from the amygdala to the BST; one is obviously through the stria terminalis, but the other is the massive ventral route through the ansa peduncularis system. These two pathways have quite different developmental histories: early on, fibers establishing the stria terminalis extend dorsally along the sulcus terminalis (the caudal edge of the telencephalic roof plate), whereas fibers establishing the ventral pathway extend rostrally through the medial ventricular ridge (see [5]); thus, the two pathways are quite distinct from the beginning. And third, it is important to recognize that other parts of the cerebral hemisphere — both cortical and nuclear — project to the BST. In summary, not all parts of the amygdala project to the BST, there are two massive and distinct pathways from the amygdala to the BST, and parts of the cerebrum other than the amygdala provide heavy inputs to the BST.

In addition to the components of the amygdala dealt with here, other regions of the cortical mantle that project directly to the BST include the accessory olfactory bulb, and major parts of the prefrontal region, insula, and hippocampal formation, at least in the rat, where these connections have been examined most thoroughly thus far. The accessory olfactory bulb projects to a discrete region within the principal nucleus of the posterior BST division [85], and as we have seen (Fig. 3), both amygdalar

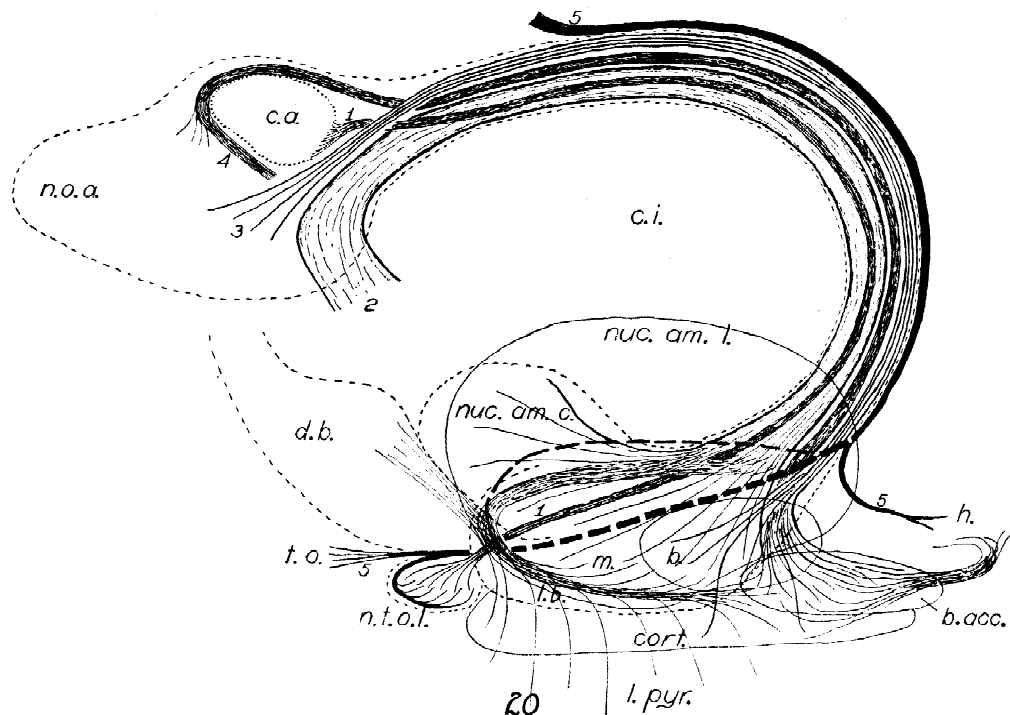


Fig. 35. Organization of the mammalian stria terminalis as illustrated for the opossum by Johnston [45]. The five major strial components discussed in the text are clearly presented (1–5) in this schematic sagittal projection, with rostral to the left, and dorsal to the top. Reproduced with permission from Ref. [45].

terminal fields of the accessory olfactory tract (the posteromedial cortical and medial nuclei), and the closely associated posterior amygdalar nucleus all massively innervate the posterior BST division, along with the medial group of the anterior division.

On the other hand, the main olfactory bulb, piriform area, and dorsal endopiriform nucleus do not seem to innervate directly the BST. Instead, such pathways arise in more caudal regions of the main olfactory cortex (in the amygdalar region) and in the tiny ventral endopiriform nucleus (Fig. 3).

The gustatory and visceral sensory areas in the dysgranular insular region also project massively to the BST, especially to the region of the oval and juxtacapsular nuclei of the anterior BST division, and associated polymodal regions of the dorsal and posterior agranular insular cortex also project more lightly to the BST [60,61,81,116]. In addition, at least two major regions of the medial prefrontal cortex, the infralimbic and prelimbic areas, appear to innervate substantially the BST. The infralimbic area projects heavily to the medial group of the anterior BST division and lightly to the posterior division (Section 5.3, Fig. 3), whereas the prelimbic area reportedly innervates the ‘posterior division of the lateral BST’, which may correspond to caudal regions of our anterolateral area [43,61,87]. However, Vertes and Todorova [114] did not observe projections from the prelimbic area to the BST. It seems likely that the medial prefrontal region in rats is much more differentiated than currently appreciated. And finally, at least two regions of the hippocampal formation, the lateral entorhinal area and ventral subiculum, project directly to the BST. Projections from the ventral subiculum to the BST are dealt with in Section 5.2, where it is pointed out that the ventral subiculum also projects densely to the parts of the medial prefrontal cortex just mentioned. Interestingly, the lateral entorhinal area also projects massively to the infralimbic and prelimbic areas (see [106]), as well as to the BST (see [61]).

To summarize, medial prefrontal and insular regions of cortex preferentially innervate the anterior BST division, with the infralimbic area further tending to innervate the medial group and the prelimbic area and insular region tending to innervate the lateral group. By contrast, the accessory olfactory bulb and hippocampal formation preferentially innervate the posterior BST division and the medial group of the anterior division. And for the sake of completeness, it should be pointed out that a number of amygdalar cell groups may influence the BST indirectly via projections ‘relayed’ through prefrontal, insular, and/or hippocampal formation cortex (see [60,74,101,107]). Such a mechanism could be especially important for regions like the lateral and anterior basolateral amygdalar nuclei that apparently do not project directly to the BST.

In closing this section it is important to emphasize that non-cortical (basal ganglia/cerebral nuclei/striatopallidum, GABAergic) parts of the cerebral hemisphere provide

massive inputs to the BST — in particular the medial and central nuclei of the amygdala, all, or most [18], of which appear to be caudal differentiations of the striatum [101,107]. At least two other regions of the striatum also appear to innervate the BST, although relatively lightly: the fundus [4] and the lateral septal nucleus [79]. And finally, there are inputs to the BST from the substantia innominata [38,64] and medial septal–diagonal band complex [105], ventral and medial components of the pallidum, respectively [101].

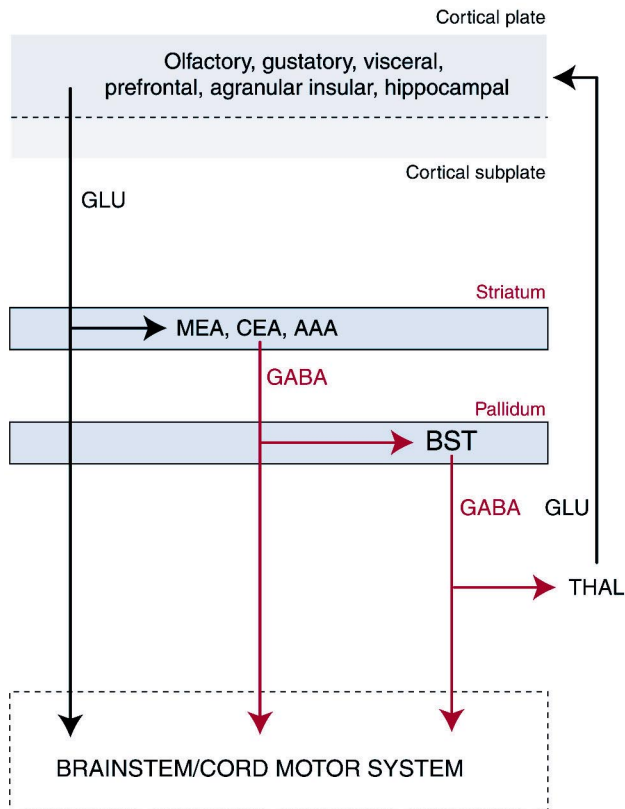
6.4. Relations between central and medial amygdalar nuclei and the BST

Recently, de Olmos and Heimer [27] have summarized the main arguments for regarding as a morphological unit the central and medial amygdalar nuclei, caudal substantia innominata, and BST — which they refer to as the extended amygdala. First and foremost, the extended amygdala is unique in the cerebral hemispheres because its components do not fit the standard striatopallidal model of participating in a ‘parallel’ cortical–basal ganglia–thalamocortical re-entrant circuit. Thus, the striatopallidal system and extended amygdala are quite distinct. In addition, extended amygdala components are highly interconnected by long ‘associative’ pathways, their functions are related to the autonomic and neuroendocrine systems, and they show certain neurochemical specializations. We have examined these arguments in detail elsewhere [14,101,107]. In brief, there is an alternative interpretation of the data. It is easy to place extended amygdala components in a standard model of the cortico–striatopallidal system, with inputs to the brainstem motor system and to a thalamocortical re-entrant system (Fig. 36); there are complex, long ‘associative’ pathways in other components of the striatopallidum as well; and neurochemical differentiations are found throughout the basal ganglia/cerebral nuclei or striatopallidum. In short, we would suggest that the central and medial nuclei of the amygdala, caudal substantia innominata, and BST are simply regions of the basal ganglia/cerebral nuclei/striatopallidum that preferentially influence visceromotor and hypothalamic response mechanisms.

This essentially theoretical debate does not, of course, detract from the main structural facts: heavy interconnections between the central/medial amygdalar nuclei, caudal substantia innominata, and BST, which have been well-known since the 1970s [28,51,105]. This work established that the relevant connections are topographically organized, and because they are exceptionally complex, knowledge about organizing principles has evolved slowly, and is undoubtedly still very incomplete. Nevertheless, the present study is the most detailed yet, and the results appear to indicate that certain earlier conclusions may need revision.

For example, it is often assumed that almost all subdivi-

A. Prototypical cortico-striatopallidal circuit



B. Differentiations

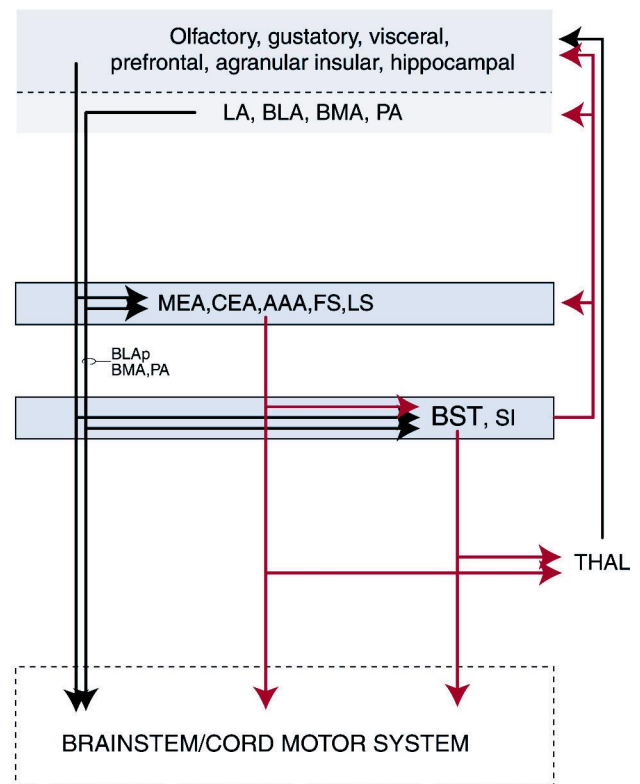


Fig. 36. The BST viewed in the context of a standard cortico–striatopallidal projection system. (A) In a prototypical or minimal cortico–striatopallidal projection (using the isocortex–dorsal striatum–globus pallidus as a model), layer 5 of cortex sends a glutamatergic projection to the motor system in the brainstem and/or spinal cord, with a collateral to the striatum; the striatum sends a descending GABAergic projection to the brainstem motor system, with a collateral to the pallidum; and the pallidum also sends a GABAergic projection to the brainstem motor system, and a collateral to thalamocortical re-entrant loops (see [101]). As discussed in the text, most of the BST (except perhaps certain anterolateral regions) fit nicely into this connectional scheme, as a rostral component of the pallidum. (B) There are a number of other connections arising within the cerebral hemispheres that supplement the basic circuitry outlined in A. As discussed in the text, additional connections such as these are also found in other regions of the striatopallidum. Projections from presumed cortical subplate regions of the amygdala to presumed striatal regions of the amygdala are discussed in Refs. [12,75,83]. In parts A and B, projections shown in red are GABAergic, and presumably inhibitory (or disinhibitory in the case of pallidal structures); whereas projections shown in black are glutamatergic and presumably excitatory.

sions of the central and medial nuclei of the amygdala have corresponding subdivisions in the lateral and medial regions of the BST, respectively (e.g., [2,3,27]). However, it is apparent from Fig. 3 that projections arising in subdivisions of the central and medial nuclei do not have a one-to-one correspondence with BST components. Instead, each subdivision of the central and medial nuclei sends divergent inputs to multiple BST cell groups, and conversely many individual BST cell groups receive inputs not only from multiple subdivisions of one nucleus or the other, but also from subdivisions of both nuclei. The latter overlap of projection fields from the medial and central nuclei is extensive in the medial group of the anterior BST division (Fig. 3).

It has also been suggested that reciprocal connections characterize specific pairs of cell groups in the central/medial nuclei and BST (e.g., [2,3,27]). However, in two

examples where this possibility has been examined carefully with the PHAL method it has not been confirmed. The first example involves the distinctive juxtacapsular nucleus in the far lateral BST. It projects heavily to the medial part of the central amygdalar nucleus [30] but receives no input from any part of the central or medial nucleus of the amygdala (Fig. 3). The second example involves the equally distinctive oval and fusiform nuclei, also in lateral regions of the BST. Both nuclei receive inputs from all three parts of the central amygdalar nucleus (Fig. 3), but each nucleus projects back selectively to the medial rather than lateral part of the central nucleus [31]. Related suggestions that corresponding parts of the central/medial amygdala and BST share similar inputs and outputs has not been subjected to detailed analysis, but there are obvious exceptions. For example, the central and medial nuclei receive massive inputs from the lateral, anterior basolater-

al, and intercalated amygdalar nuclei, and the dorsal endopiriform nucleus (see [8,69,77]), none of which project to the BST.

Finally, the suggestion that there are two distinct subdivisions of the extended amygdala, one associated with the central nucleus and its terminal fields in the substantia innominata and BST and the other associated with the medial nucleus and its terminal fields in the same two structures, needs to be examined carefully. Obviously, the central and medial nuclei of the amygdala are separate structures, but how distinct their outputs remain is another matter. It was mentioned earlier in this Section that there is considerable overlap of terminal fields from both nuclei in the medial group of the anterior BST division (Fig. 3), and it is also clear that fibers and terminal fields in the substantia innominata overlap very considerably for the central nucleus (see levels 22 and 23 in Figs. 6–9) and for certain parts of the medial nucleus (see levels 22 and 23 in Figs. 11, 13 and 14) — although it is worth noting that the important posterodorsal part of the medial nucleus barely innervates the substantia innominata at all (see Figs. 14 and 33).

6.5. Summary and conclusions

The BST form a highly differentiated region of the basal or non-cortical division of the cerebral hemisphere. During embryogenesis at least the bulk of the BST develop in the medial ventricular ridge [5,7], where their neurons are among the earliest born in the cerebral hemispheres — along with those in the globus pallidus, substantia innominata, and medial septal–diagonal band complex [110]. Furthermore, as with the other cell groups just listed, most adult BST neurons are GABAergic [17,96]. Together, these features suggest that the BST are a rostral differentiation of the pallidum, which is supported by the basic organization of their connections (Fig. 36) [101,107,108]. However, there currently is no definitive way to draw a precise border between all striatal and pallidal components, and there is morphological and histochemical evidence to suggest that at least some of the anterolateral BST adjacent to the caudoputamen is striatal (see [18,59,61]).

Like the well-known dorsal striatopallidal system, the BST receive massive GABAergic inputs from what appear to be caudal differentiations of the striatum, the central and medial nuclei of the amygdala (see [101,108]), with the former innervating the anterior BST division and the latter innervating most densely the posterior BST division. However, particular regions of the BST may receive inputs from multiple regions of striatum, just as, for example, the external globus pallidus receives inputs from both the caudoputamen [70] and nucleus accumbens [103,112]. Thus, the medial amygdalar nucleus also projects to the medial group of the anterior BST division, and the BST receive inputs from other regions of the striatum as well,

including the fundus (ventral striatum) and lateral septal nucleus (medial striatum), although they are much lighter than those from the central and medial nuclei of the amygdala (Section 6.3).

Like other parts of the striatum, the central and medial amygdalar nuclei receive massive, direct glutamatergic inputs from the cerebral cortex. As reviewed in detail elsewhere [60,101], the central nucleus is massively innervated by visceral, gustatory, and agranular insular regions of cortex, and moderately innervated by the medial prefrontal region and subiculum; whereas the medial nucleus is massively and uniquely innervated by the accessory olfactory cortex, as well as by main olfactory, medial prefrontal, agranular insular, subicular, and entorhinal areas. Similar partial convergence of different cortical areas upon particular regions is common throughout the striatum (reviewed in [101]).

Thus, the BST receive a massive GABAergic input from the striatum (central and medial amygdalar nuclei), which in turn receive a massive glutamatergic input from the cerebral cortex — and the BST in turn project to brainstem motor systems and thalamocortical re-entrant loops. This is fundamentally similar to the organization of the isocortical–dorsal striatopallidal system. In addition, the BST receive a substantial direct input from the cerebral cortex itself, as occurs for other pallidal regions as well. For example, frontal cortex projects to the internal and external segments of the globus pallidus [66], and parts of the orbitofrontal, agranular insular, and olfactory cortex project to the substantia innominata [9,37,82]. The best known, and quantitatively most abundant, cortical inputs to the BST arise in main and accessory olfactory-related parts of the amygdala (Figs. 1 and 3), but other important sources include dysgranular gustatory and visceral regions of the insular region, medial prefrontal and agranular insular association areas, and the ventral subiculum and lateral entorhinal area of the hippocampal formation (Section 6.3).

The most obvious remaining question concerns the precise organization of BST projections. We are currently analyzing a collection of about 150 PHAL injections throughout all regions of the BST, but the answer is not yet known. From what has been published thus far, however, it seems likely that the three major regions of the BST that are differentiated in Fig. 3 have qualitatively different sets of projections. These three regions are the posterior division, and the medial and lateral groups of the anterior division. Incomplete analyses to date suggest that the posterior division innervates especially densely the hypothalamic medial nuclei [95], the medial group of the anterior division preferentially innervates the hypothalamic periventricular region and perifornical region of the hypothalamic lateral zone [68,80,84,99,111], and the lateral group of the anterior division preferentially innervates hypothalamic and lower brainstem regions associated with the autonomic system, along with particular regions of the

ventral tegmental area, substantia nigra, and retrorubral area [29–31,42,63,86,113].

Much current thinking, including our own, is heavily influenced by comparative analyses of the vertebrate forebrain basic plan by J.B. Johnston, who published his final synthesis in 1923 [45]. However, the neuroanatomy revolution of the 1970s has led to an almost complete revision of every major assumption about the structural organization of the nervous system, including the cerebral hemispheres, and especially the limbic parts of Broca and MacLean [101]. By far the most data has been gathered in the rat and here the results bear no resemblance to Johnston's conclusions — which were based simply on non-experimental histological stains for fibers and cells — and many homologies of forebrain parts between the various classes of vertebrates remain controversial. For example, Johnston identified a morphological entity called the bed of the stria terminalis as the gray matter forming a bridge between rostral and caudal olfactory regions, and including, progressively, what we now call the anterior olfactory nucleus, nucleus accumbens and olfactory tubercle, BST, substantia innominata, and amygdala. No one today regards these particular structures as a morphological entity, and no one would agree (at least in the rat) with Johnston's description of, to pick just one typical example, the central nucleus: 'The central nucleus is the most direct avenue of continuity with anterior olfactory areas . . . Its chief fiber tract is the olfactory projection tract, but it has fiber connections with the pyriform cortex and possibly with the lentiform nucleus.' (Ref. [45], p. 477). As a result, there are at this point in time at least two different models of cerebral hemisphere organization. One regards the extended amygdala as a morphological and functional entity that is an odd part of the cerebral hemispheres because it does not participate in thalamocortical re-entrant loops and displays other structural and chemical differentiations as well. The other model views the extended amygdala simply as part of a cortico–striatopallidal (cerebral) system that is differentiated for modulating visceral and hypothalamic responses. More data is needed to validate one model or the other, or to generate an alternative, better model.

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