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Review

The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness

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Abstract

The thalamic midline and intralaminar nuclei, long thought to be a non-specific arousing system in the brain, have been shown to be involved in separate and specific brain functions, such as specific cognitive, sensory and motor functions. Fundamental to the participation of the midline and intralaminar nuclei in such diverse functions seems to be a role in awareness. It is unknown whether the midline and intralaminar nuclei, together often referred to as the 'non-specific' nuclei of the thalamus, act together or whether each nucleus is involved idiosyncratically in separate circuits underlying cortical processes. Detailed knowledge of the connectivity of each of these nuclei is needed to judge the nature of their contribution to cortical functioning. The present account provides an overview of the results of neuroanatomical tracing studies on the connections of the individual intralaminar and midline thalamic nuclei in the rat, that have been performed over the past decade in our laboratory. The results are discussed together with those reported by other laboratories, and with those obtained in other species. On the basis of the patterns of the afferent and efferent projections, we conclude that the midline and intralaminar thalamic nuclei can be clustered into four groups. Each of the groups can be shown to have its own set of target and input structures, both cortically and subcortically. These anatomical relationships, in combination with functional studies in animals and in humans, lead us to propose that the midline and intralaminar nuclei as a whole play a role in awareness, with each of the groups subserving a role in a different aspect of awareness. The following groups can be discerned: (1) a dorsal group, consisting of the paraventricular, parataenial and intermediodorsal nuclei, involved in viscero-limbic functions; (2) a lateral group, comprising the central lateral and paracentral nuclei and the anterior part of the central medial nucleus, involved in cognitive functions; (3) a ventral group, made up of the reuniens and rhomboid nucleus and the posterior part of the central medial nucleus, involved in multimodal sensory processing; (4) a posterior group, consisting of the centre médian and parafascicular nuclei, involved in limbic motor functions.

Theme: Other systems of the CNS

Topic: Association cortex and thalamocortical relations

Keywords: Thalamus

Abbreviations: BDA, biotinylated dextran amine; CeM, central medial nucleus; CL, central lateral nucleus; CM, centre médian nucleus; IMD, intermediodorsal nucleus; PC, paracentral nucleus; Pf, parafascicular nucleus; PHA-L, *Phaseolus vulgaris*-leucoagglutinin; Pt, parataenial nucleus; PV, paraventricular nucleus; Re, reuniens nucleus; Rh, rhomboid nucleus

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Contents

1. Introduction

1.1. Specificity vs. non-specificity

The intralaminar and midline nuclei of the thalamus have long been considered to exert a global influence on cortical functioning. This thought has been challenged in recent years, however, on the basis of anatomical [11–13], clinical [87,88,152–154] and behavioral data [131]. The present paper attempts to extend the notion of the 'specificity of the non-specific nuclei' [11,47] by proposing that these nuclei can be clustered in terms of their patterns of connectivity, suggesting functional homogeneity within these clusters and differences in function between them. First, the patterns of inputs and outputs of the intralaminar and midline nuclei of the rat are described, with special attention to evidence of topographical differences between efferent fibers emanating from individual nuclei. Subsequently, functional data and views with respect to particular parts of the midline and intralaminar complex will be considered.

The concept of the non-specificity of the intralaminar and midline thalamic nuclei originated from three sets of observations. First, this constellation of nuclei receives an extensive input from the mesencephalic, pontine and medullary reticular formation, which was thought to be rather non-discriminatory with respect to individual nuclei [27,51,94]. Second, the output of these nuclei to cortical target fields was described as diffuse and non-specific [67]. Third, electrophysiological stimulation of these regions in the thalamus causes the so-called cortical recruiting effect [62,91]. Low-frequency stimulation causes slow-wave activity in the entire cortical mantle accompanied by somnolence, whereas high-frequency stimulation results in desynchronised cortical activity and arousal, leading into epileptiform activity when the stimulation is intense [58,61].

Originally, adjacent nuclei such as the medial dorsal, pulvinar and ventral anterior nuclei were considered part of the non-specific group of nuclei on the basis of this recruiting effect, but later data have dissociated these nuclei from the intralaminar and midline nuclei based on laminar distribution patterns of their efferents and afferents [46,48,56].

1.2. Arousal and awareness

Because of their strong brainstem inputs, the intralaminar and midline nuclei are considered as part of the ascending reticular activating system (ARAS), the rostral continuation of the reticular formation. For instance, it has been shown that intralaminar neurons receive monosynaptic input from the mesencephalic reticular formation and in turn connect monosynaptically with many cortical areas [143]. In line with this are functional imaging studies, showing that activation of thalamic nuclei is related to higher levels of wakefulness [41,72,77,84,109].

In the words of Llinas and Paré, the intralaminar and midline nuclei serve to generate intrinsic functional modes, leading to wakefulness that is independent of the absence or presence of sensory stimulation [81]. This wakeful functional mode of the brain would allow for faster execution or greater efficiency of cortical processing [140], or lower thresholds for cortical activation by incoming stimuli [61,68]. In other words, intralaminar/midline-induced cortical activation would lead to greater vigilance, necessary for awareness of incoming information. It is important to stress that the midline and intralaminar nuclei do not 'produce' awareness, but rather provide the necessary arousal of cortical and subcortical regions supporting information processing that is correlated with awareness [142]. The intralaminar and midline nuclei can be thought to facilitate the entry into a functional mode, involved, as Jasper states, in ''the control of states of consciousness and perceptual awareness'' rather than dealing with the contents of awareness per se [63].

A role for the intralaminar and midline structures in awareness of stimuli of various sensory modalities has been proposed [139]. Evidence pertaining to the involvement of the intralaminar and midline nuclei in auditory vigilance, comes from a positron emission tomography study investigating sustained attention [105]. In this test, vigilance was measured by asking the subjects to attend for a duration of 60 min to a possibly occurring sudden intensity drop. It appeared that the level of activation of the midline and intralaminar nuclei, together with that of the anterior cingulate cortex, correlated with the level of vigilance. Similarly, it was postulated that the intralaminar nuclei play a role in visual awareness [110], in line with thalamic activation found in functional imaging paradigms of visual attention [138,144]. Animal experiments indicating a role in visual awareness show ocular and cephalic movements towards visual stimuli in both cats and monkeys, coinciding with electrophysiological activity recorded from the intralaminar region; alternatively, electrical stimulation of the intralaminar nuclei causes head movements and increased electrophysiological response to visual stimuli [57,134,135]. In accord with a role

for the intralaminar and midline nuclei in visual awareness and the response to visual stimuli, Schiff et al. [133] describe oculogyric crises as a pathological state of this complex. They state that aberrant monoaminergic and cholinergic input causes 'dystonia' of the intralaminar-midline complex. This leads to a syndrome characterized by fixed eye deviation, thought disorder, and postural and autonomic disturbances, together called the Von Economo crisis. The combination of such seemingly disparate symptoms fit with the widespread anatomical connectivity of these nuclei as a group.

A role in the awareness of tactile and nociceptive information has been described as well for the midline and intralaminar nuclei. This derives from the anatomical evidence that the above nuclei receive nociceptive input from the spinothalamic and spinoreticulothalamic projections [144,44,107], from electrophysiological experiments showing that these nuclei respond to noxious stimuli [37] and from functional imaging studies showing thalamic activation in vibrotactile perception [65] and pain modulation [53]. In turn, the intralaminar and midline nuclei project to the cingulate area, which has been taken to mean that their role is related to the affective processing of the incoming tactile or nociceptive information [111,161].

1.3. Scope of this article

Rather than ascribing to the intralaminar and midline nuclei of the thalamus a uniform function, Bentivoglio et al. [11] and Groenewegen and Berendse [47] have argued that, although the inputs to the diverse thalamic structures may be partly overlapping, the output is organized in segregated and parallel pathways. In this way, the general effects on cortical functioning of the intralaminar and midline nuclei can be thought to arise from a concerted influence of the individual nuclei on the various cortical areas. On the other hand, the selective pattern of cortical inputs and outputs of these nuclei warrant the assumption that they might also exert more specific influences on selective cortical areas, as evidenced for instance by the fact that single intralaminar cells receiving midbrain afferents each have particular cortical targets instead of projecting to multiple areas [143]. Recently, we have added that in addition to differences in the patterns of projection arising from the various midline and intralaminar nuclei, the pattern of projections from a single nucleus may also differ for subregions in that nucleus [35,153]. This offers the possibility of even more fine-grained influences on cortical functioning. Knowledge of the anatomical specificity of connections of the midline and intralaminar nuclei will allow the prediction of the roles that these nuclei may play in normal brain functioning and diseases of the brain.

This review therefore offers an overview of afferent and efferent connections of the individual midline and intralaminar nuclei in the rat, founded on the large database of injections of anterograde tracers made in these nuclei of the thalamus over the last decade in our laboratory. Some cases have been used for studies published previously [12,13,35,47,165–167]. For nuclei where information was lacking, we made additional injections. In the analysis of the results, special attention was paid to topographical differences in the patterns of projection from different parts of the nuclei. This could only be done in reasonably large nuclei, with rostro-caudal, medio-lateral or dorso-ventral dimensions that allow differential placement of the tracer injections; this was the case for the paraventricular, the reuniens, the intermediodorsal, and the central medial nuclei.

2. Materials and methods

2.1. Injections

The collection of cases with injections of anterograde tracers in the midline and intralaminar thalamic nuclei consisted of 128 female Wistar rats (Harlan/CPB, Zeist, The Netherlands). Of these, eight injections were made specifically for the present study, the remaining cases were taken from studies published previously. Most of these earlier studies were focused on particular aspects of the organization of the outputs of the midline and intralaminar thalamic nuclei, i.e., specifically their projections to the cerebral cortex and the striatum [12,13,166,167] or the limbic cortices [35,165]. The present account aims to provide a comprehensive description of all projections of the midline/intralaminar complex.

In all experiments the procedure followed was similar. In the following, the methodology used for the eight new cases is described, for experimental details of the previous cases the reader is referred to the original articles (see references above). Experimental procedures were all approved by the local Committee on the Ethics of Animal Experimentation of the Vrije Universiteit. Rats weighing between 180 and 230 g were deeply anesthetized with a (4:3) mixture of Aescoket (1% ketaminum·HCl, Aesculaap, The Netherlands) and Rompun (2% xylathine·HCl; Bayer, Belgium), using an intramuscular injection (0.1 ml/100 g body weight). Rats were then mounted in a stereotaxic apparatus, the brain was exposed through small burr holes and injections of anterograde tracers were made at coordinates derived from the atlas of Paxinos and Watson [106].

The tracers *Phaseolus vulgaris*-leucoagglutinin (PHA-L) and biotinylated dextran amine (BDA) were used. Deposition of the tracers was performed iontophoretically using glass micropipettes (internal diameter 10–25 μm). Pipettes were filled with 5% BDA in 0.01 M phosphate buffer (PB) or 2.5% PHA-L in 0.1 M phosphate-buffered saline (PBS), pH 7.4, and tracer was deposited over a 10–30 min period using a positive-pulsed square wave current (7 s on, 7 s

off; CCS-3 current source, Midgard, USA). For PHA-L injections a current of 7.5–9.0 μA was used, for the BDA injections the current was 6.5–7.0 μA. Post-injection survival times ranged from 7 to 14 days. Following this period the animals were deeply anesthetized with Nembutal (sodiumpentobarbital 1 ml/kg; Sanofi, The Netherlands), and perfused with 300 ml of heparinized NaCl solution (0.9%) followed by 400 ml of paraformaldehyde fixative (4% in 0.1 M PB, pH 7.4). Brains were removed from the skull, post-fixed for 1–2 h in 4% paraformaldehyde, and stored for at least 16 h in 20% glycerol–2% (v/v) dimethylsulfoxide (DMSO) in PB at 4 °C. Forty μm thick coronal sections were then cut on a freezing microtome. Tissue was collected sequentially in six receptacles that contained either 0.05 M Tris–HCl buffered saline (pH 7.60) with 0.5% Triton X-100 (TBS-T), if used immediately for (immuno)histochemistry, or glycerol–DMSO solution (for storage at −20 °C). In some cases, prior to (immuno)histochemistry, sections were rinsed three times in 0.05 M Tris–HCl buffered saline, pH 7.6 (TBS), treated with 1% H_2O_2 in TBS for 10 min, and rinsed again (once with TBS and twice with TBS-T) to reduce endogenous peroxidase activity.

2.2. Anterograde tracer histochemistry

In all cases, histochemical procedures were used to detect each tracer (BDA or PHA-L) individually. For visualization of BDA, tissue sections were rinsed three times with TBS-T and incubated (at room temperature unless otherwise specified) for 1.5 h with TBS-T and a (1:1) mixture of reagents A (avidin DH) and B (biotinylated horseradish peroxidase H complex) from the Vectastain ABC kit (Vector Laboratories, USA). The AB solution (8 μl A and 8 μl B per ml TBS-T) was allowed to stand for 30 min prior to use. After incubation with AB, sections were rinsed twice with TBS-T and twice with TBS, or twice with 0.1 M PB (pH 7.4), prior to visualization of the BDA–AB complex peroxidase activity. TBS rinsed sections were processed using a TBS solution containing 0.05% 3′,3-diaminobenzidine (DAB) and 0.0015% H_2O_2 for visualization of peroxidase activity as a brown reaction product. PB rinsed sections were treated with a PB solution containing 0.05% DAB plus 0.5% nickel ammonium sulphate (DAB-Ni) and 0.0015% H_2O_2 for visualization of peroxidase activity as a blue–black reaction product. Color development was allowed to proceed for 5–15 min after which sections were rinsed with TBS, mounted on glass slides from 0.05 M Tris–HCl, pH 7.6 containing 0.2% (w/v) gelatin, and dried. For determination of injection location and examination of labeled fibers, sections were counterstained for Nissl substance with 0.3% cresyl violet (in H_2O). Finally, the material was dehydrated through an ethanol gradient, and coverslipped from xylene using Permamount.

The tracer PHA-L was detected in tissue sections using the peroxidase anti-peroxidase (PAP) method. Sections were rinsed with TBS-T as above and incubated with a rabbit anti-PHA-L serum (αPHA-L, diluted 1:2000 in TBS-T; Dakopatts, Denmark) for 18 h at 4 °C. After three rinses with TBS-T, sections were incubated in TBS-T containing a swine anti-rabbit serum (SwαR; 1:50 from Nordic, the Netherlands; or 1:100 from Dakopatts) for 45 min, further rinsed with TBS-T, and finally incubated with rabbit (r)-PAP (Dako, Denmark) diluted 1:800 in TBS-T for 45 min. After the final rinses (TBS or PB), peroxidase activity was visualized as above with DAB or DAB-Ni as chromogen. Sections were also counterstained and coverslipped as above.

Nomenclature and abbreviations of the midline and intralaminar nuclei follows that used by Berendse and Groenewegen [12,13]. The nomenclature and abbreviations used for the cortical and subcortical target areas is taken from Swanson [146], with the exception of the use of ACCv/d for the anterior cingulate cortex, ventral and dorsal parts, respectively, which is taken from Jones and Witter [66].

3. Anatomy of the intralaminar and midline nuclei of the thalamus

Together, the intralaminar and midline nuclei form a conspicuous arrangement of nuclei in the medial dorsal part of the rat thalamic complex (Fig. 1). The midline nuclei, as the name implies, are located medially in the thalamus as a thin strip of cells, spanning the entire dorsal-to-ventral extension of the thalamus. The intralaminar nuclei are located lateral to the mediodorsal nucleus of the thalamus and contained within the internal medullary lamina, a thin sheet of white matter.

3.1. Midline nuclei of the thalamus

The midline nuclei of the thalamus comprise the paraventricular, parataenial, intermediodorsal, reuniens and rhomboid nuclei. Together they occupy the midline of the rat thalamus from its very rostral tip to approximately one-third of the total length of the thalamus.

3.1.1. Paraventricular nucleus

3.1.1.1. Location and morphology. The paraventricular nucleus of the thalamus (PV) is located medially in the rat thalamus, spanning the entire rostrocaudal length of the midline/intralaminar complex. The PV lies dorsal and medial to the mediodorsal nucleus and directly ventral to the third ventricle. Rostrally, it follows the surface of the massa intermedia and curves ventrally to form a wedge between the anterior poles of the nucleus reuniens [80]. At caudal levels, it curves and ends ventral to the habenular nuclei. Phylogenetically, the PV originates from a pronu-

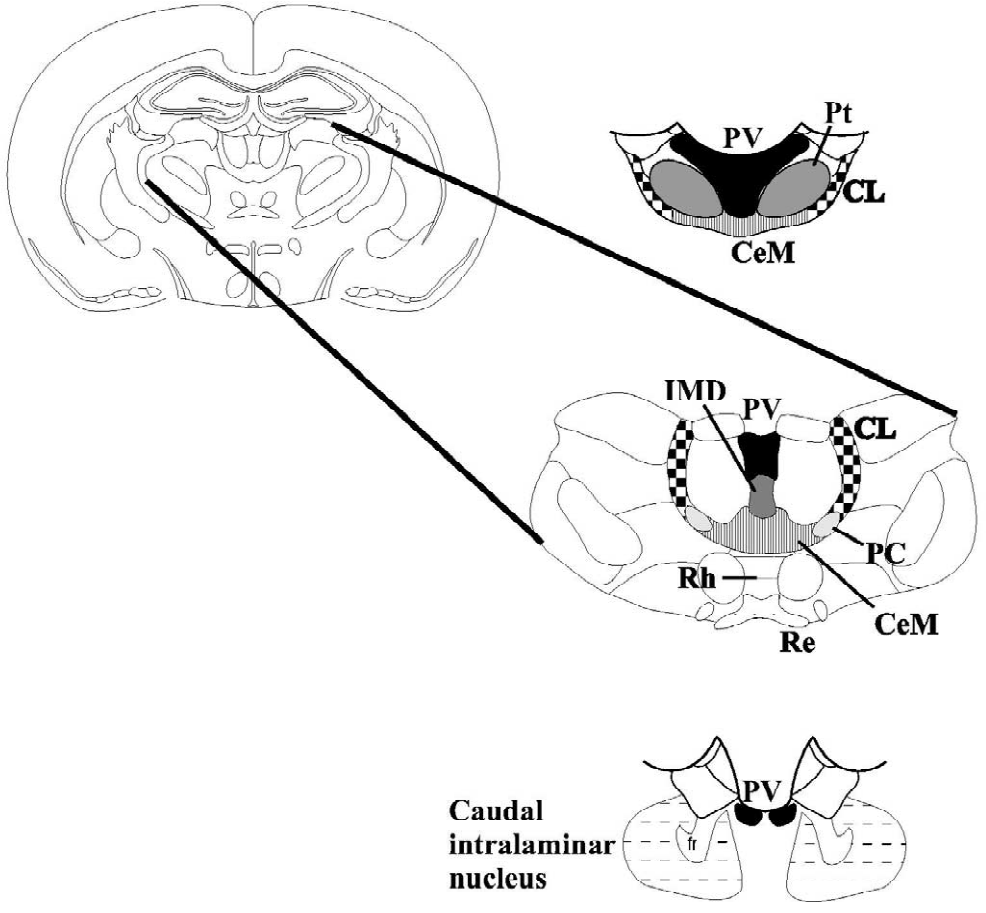


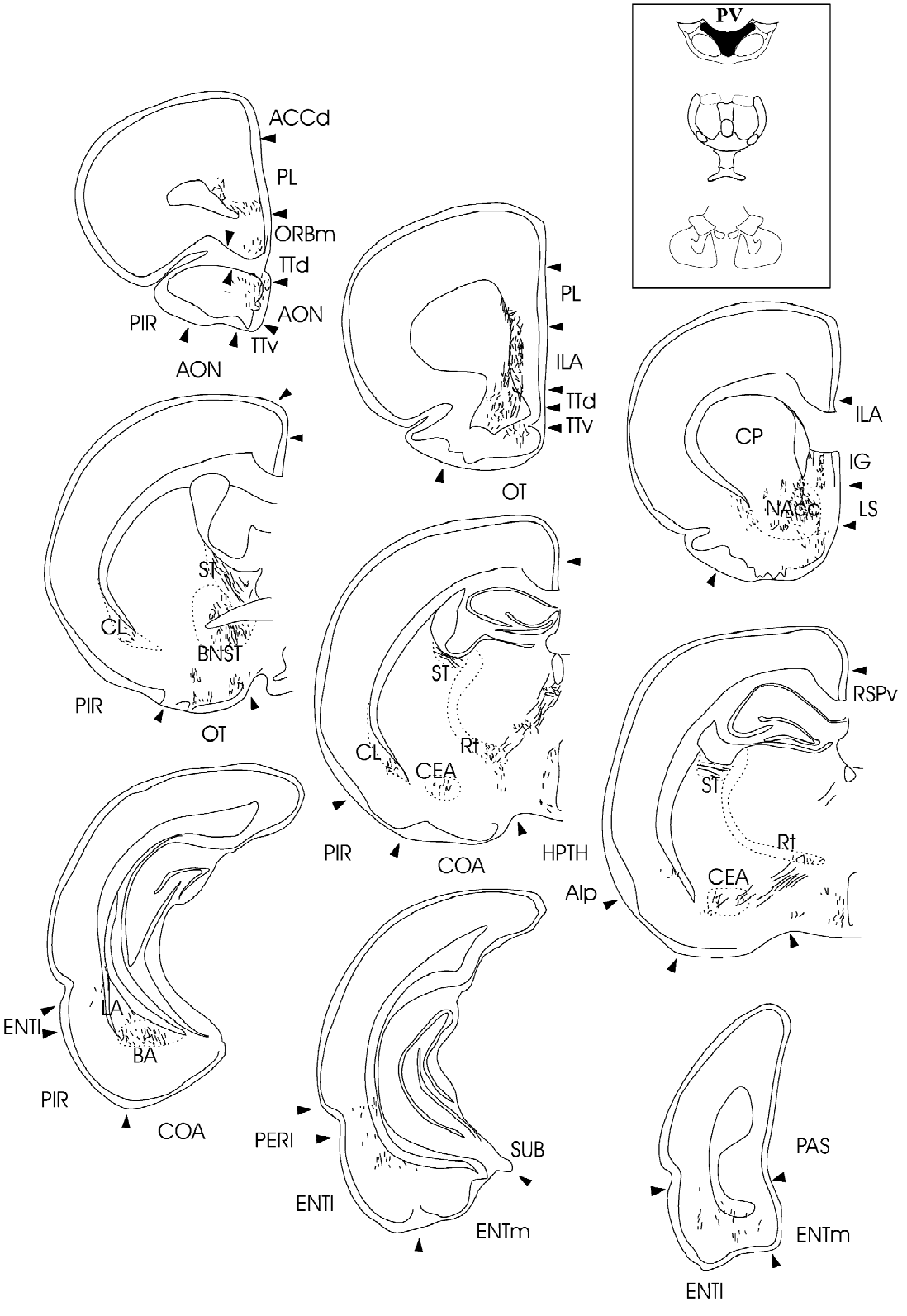
Fig. 1. Schematic representation of the midline and intralaminar nuclei in the rat brain. Each nucleus described in the text is indicated with a different shading.

clear mass that also gives rise to the pineal and the habenular nuclei. Because of this, Jones [68] considers the PV to be part of the epithalamus.

3.1.1.2. Input. Anterograde and retrograde tracing studies in rats [23,27,46,59,97–99,103,123,136,147,156] have revealed that the PV receives a strong aminergic input consisting of a histaminergic input from the tuberomammillary nucleus, a dense dopaminergic input from the ventral tegmental area and the retrorubral region, a noradrenergic input from the locus coeruleus and the nucleus of the solitary tract, and a serotonergic input from the dorsal raphé. In addition, the PV receives input from the parabrachial nucleus, bed nucleus of the stria terminalis, dorsomedial hypothalamus and the supramammillary nuclei. Inputs from the amygdalar complex originate in the central nucleus. Cortical input is derived from the infralimbic cortex and the subiculum.

In monkeys, studies have been scarce but are consistent with the rat studies [1,113]. Slight differences are found in hippocampo-thalamic projections, where apart from the subiculum also the entorhinal cortex projects to the PV.

Fig. 2. Overview of the pattern of terminal and passing fiber labeling following a representative injection of the anterograde tracer PHA-L in the paraventricular nucleus of the rat thalamus. Terminating fibers are indicated as curved lines, passing fibers as straight lines. Abbreviations: ACCd—dorsal anterior cingulate cortex; ACCv—ventral anterior cingulate cortex; AId—dorsal agranular insular cortex; AIv—ventral agranular insular cortex; AIp—posterior agranular insular cortex; AON—anterior olfactory nucleus; AUD—auditory cortex; BA—basal amygdala; BNST—bed nucleus of the stria terminalis; CEA—central nucleus of the amygdala; CL—claustrum; COA—cortical nucleus of the amygdala; CP—caudate putamen; ENTm—medial entorhinal cortex; ENTl—lateral entorhinal cortex; EP—endopiriform nucleus; FS—fundus striatum; GU—gustatory cortex; HPC—hippocampus; HPTH—hypothalamus; IG—induseum griseum; ILA—infralimbic cortex; LA—lateral amygdala; LS—lateral septal nucleus; MOp—primary motor cortex; MOs—secondary motor cortex; NAcc—nucleus accumbens; ORBl—lateral orbital cortex; ORBm—medial orbital cortex; OT—olfactory tubercle; PAR—parietal cortex; PAS—parasubiculum; PERI—perirhinal cortex; PIR—piriform cortex; PL—prelimbic cortex; POR—Postrhinal cortex; POST—postsubiculum; RSPd—dorsal retrosplenial cortex; RSPv—ventral retrosplenial cortex; Rt—reticular thalamic nucleus; SSp—primary somatosensory cortex; SSs—secondary somatosensory cortex; ST—stria terminalis; SUB—subiculum; TTd—taenia tecta dorsalis; TTv—taenia tecta ventralis; VIS—visual cortex; VISC—visceral cortex.


PV
ACCd
PL
ORBm
TTd
AON
PIR
TTv
AON
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ENTm
ENTl

Additionally, in contrast to rats, Aggleton and Mishkin [2] found no evidence for input from any of the amygdalar nuclei in the monkey.

We analyzed 30 injections of anterograde tracer substances in the PV together covering the entire rostro-caudal extent of the nucleus. Some of these were taken from previous studies [12,13,166], the others were prepared and analyzed for this study.

3.1.1.3. Trajectory of efferent fibers. In all cases, we observed a rather uniform distribution of labeled fibers to their respective targets. Several trajectories are used by the fibers arising from the PV en route to their target areas. A large number of fibers travels ventrolaterally from the injection site towards the basal forebrain from where some fibers course towards the amygdala and on to the rhinal cortices. Another part of the fibers turns rostrally from the basal forebrain to enter the bed nucleus of the stria terminalis and the ventral striatum. Through the bed nucleus of the stria terminalis the remaining fibers enter the stria terminalis. Via the stria terminalis, the fibers are conveyed to the amygdala, the rhinal cortices and the ventral subiculum. Fibers destined for the hypothalamus mainly travel through the anterior pole of the PV and descend along the periventricular surface. A small number of fibers exits the PV ventrally and traverses the midline thalamus to also reach the hypothalamic area.

3.1.1.4. Terminal labeling. Unless otherwise indicated, all cases show similar patterns of terminal fiber labeling, regardless of rostral, caudal, dorsal or ventral tracer placement in the PV. A representative case is shown in Fig. 2.

Cerebral cortex Within the prefrontal cortex, labeling is found in all layers of the infralimbic cortex and in the deep layers of the prelimbic cortex. Incidentally, sparse labeling is found in the anterior cingulate cortex and medial orbital cortex. The taenia tecta and anterior olfactory nucleus consistently receive moderately dense plexi of terminating fibers.

Some cases show labeling in the deep layers of the perirhinal cortex, both rostrally and caudally. The entorhinal cortex is labeled sparsely but consistently in all cases. Labeling is confined to layers III and VI of the lateral entorhinal cortex and layer III of the medial entorhinal cortex. In a few cases, the pre- and parasubiculum and the molecular and pyramidal layers of the ventral subiculum are labeled (not illustrated). A topography is evident in the terminations found in the pre- and parasubiculum and the subiculum, with injections in the anterior and dorsal parts of the PV supplying heavier fiber labeling.

Subcortical telencephalic structures The striatum is labeled in a patchy fashion, the sparsely innervated core region of the nucleus accumbens standing out clearly against the densely labeled shell, with the latter showing the highest density in its caudomedial part. Fibers extend into the adjacent part of the caudate putamen and further caudally into the subcommissural striatal cell pocket.

In the amygdaloid complex and the bed nucleus of the stria terminalis moderately dense plexi can be seen. The bed nucleus of the stria terminalis receives fibers in its lateral part mainly. The central, medial, basolateral and basomedial nuclei of the amygdala are labeled moderately densely in all cases. Few fibers are found in the claustrum

Diencephalon In the thalamus, a few labeled fibers are observed in the parataenial nucleus, mediodorsal nucleus, intermediodorsalis nucleus, rhomboid nucleus and reuniens nucleus. In the rostral ventromedial part of the reticular nucleus of the thalamus a plexus of labeled fibers is present.

Fibers innervating the hypothalamus originate in the dorsal PV mainly. In the hypothalamus, PV fibers are found in the preoptic area, the suprachiasmatic nucleus, the medial preoptic nucleus, the paraventricular hypothalamic nucleus, the central part of the anterior hypothalamic nucleus, the lateral hypothalamic area, the arcuate nucleus, the dorsomedial hypothalamic nucleus, the central part of the ventromedial nucleus, the ventral part of the posterior medial nucleus, and the posterior hypothalamic nucleus.

3.1.1.5. Comparison with previous reports and other species. Projection patterns of the PV in the rat have been described by others and the patterns of labeling presented here concur strongly with these earlier findings [8,28,90,100,101,124,148,149,168]. The only exception is the intrathalamic labeling of other midline structures that has not been described previously to our knowledge.

Reports on other species are scarce and incomplete. Nevertheless, the results obtained seem highly consistent: in monkeys, projections to the subiculum, entorhinal cortex, anterior cingulate cortex similar to the pattern of labeling shown here have been described [3,60,160].

In cats, projections to the parahippocampal cortices and anterior cingulate cortex exist [170]. In contrast to rats, however, weak labeling of the posterior cingulate cortex has been noted [98]. The strong projection to the medial nucleus accumbens has also been found [64]. Similarly, the labeling of the cat amygdala parallels that observed in rats as described by Ottersen and Ben-Ari [101] and in the present results.

3.1.2. Parataenial nucleus

3.1.2.1. Location and morphology. The parataenial nucleus (PT) in rats is a slender elongated nucleus located in the anterior half of the dorsal thalamus, where it lies in close proximity and lateral to the PV. Towards its posterior end, it fuses with the mediodorsal nucleus of the thalamus. It is thought to originate together with the mediodorsal and

the reuniens nuclei from a common nuclear mass. In man, it is reduced to a thin strip of cells lying dorsally to the large mediodorsal nucleus [68].

3.1.2.2. Input. Few studies have been devoted to the input of the PT. Because of its small size, injections of retrograde tracers in the area of the PT almost always involve neighboring structures. In anterograde studies, the PT is frequently overlooked or not mentioned.

Cortical input arises from the infralimbic cortex [59,136] reaching mainly the dorsomedial part of the PT. In addition, Chen and Su [23] describe input from the ventral subiculum and the rostral half of the claustrum.

Input from other telencephalic and diencephalic areas is judged to be very weak: the lateral septal nuclei, the bed nucleus of the stria terminalis, medial amygdala, amygdalohippocampal area, a band between ventral pallidum and nucleus accumbens, the reticular nucleus of the thalamus, the zona incerta and the suprachiasmatic nucleus as well as scattered regions throughout the hypothalamus [23]. The PT appears to receive moderate to weak brain stem input from the dorsal and median raphé nuclei, central grey, locus coeruleus, parabrachial nucleus, laterodorsal tegmental nucleus, and the nucleus of the solitary tract [15,23,27,94].

We base our descriptions on six injections of anterograde tracers in the PT, consisting of cases ($n=2$) taken from Berendse and Groenewegen [12,13] and previously unpublished ones ($n=4$). A representative case is illustrated in Fig. 3, adapted from Berendse and Groenewegen [13].

3.1.2.3. Trajectory of efferent fibers. Most fibers course anteriorly from the injection site and either enter the stria terminalis or exit the thalamus ventrally at its very rostral tip. Subsequently, they, curve anteriorly and project into the striatum or go on towards the medial prefrontal cortical areas. No fibers taking the ventral thalamic peduncle can be detected, in contrast to the fibers originating from the PV.

3.1.2.4. Terminal labeling. In general, the patterns of labeled fibers are highly similar for the different cases examined.

Cerebral cortex The densest cortical terminations are consistently found in the ventral prelimbic cortex and to a lesser extent in the infralimbic cortex. The terminal field in the prelimbic cortex extends into the medial orbital cortex at rostral levels. The terminating fibers are distributed in layers I, III and V in equal density. A moderate labeling of the agranular insular area is observed, most densely in layer I. More caudally, labeling in the superficial layer of the perirhinal cortex is seen, but this is not continuous with that in the agranular insular area. There is moderate labeling in the lateral entorhinal cortex and only some fibers are labeled in the molecular layer of the ventral subiculum.

Subcortical telencephalic structures Injections in the PT result in fiber labeling of the same regions of the ventral striatum as the paraventricular nucleus, but less dense: all cases show fibers in the ventral medial part of the striatum, i.e., the nucleus accumbens, and the lateral ventral striatum. Labeling in the nucleus accumbens is stronger in the shell than in the core.

Sparse labeled fibers in virtually all subnuclei of the amygdala can be seen.

Diencephalon Fibers terminating in the reticular nucleus of the thalamus are scarce and inconsistent across cases. When present, the few fibers are located even more rostrally than the efferents of the other midline nuclei.

3.1.2.5. Comparison with previous reports and other species. Several anterograde and many retrograde tracing studies provide information about the projection patterns of the PT in the rat [8,9,20,50,67,75,79,100,101,114,145,168], cat [64,93,95] and monkey [3,60]. The patterns of projections described in these studies are largely similar to those presented here, regardless of species. A few exceptions are found in sparse projections to the ventral and lateral orbital cortex and anterior cingulate cortex described by some authors for the rat [50,67] and cat [93,95]. In monkeys a significant projection to the anterior cingulate cortex has been found [160]. Contrasting with the diffuse projection to the amygdalar nuclei shown here, a selective projection to the central medial nucleus of the amygdala has been described in the cat [124].

In conclusion, the different studies agree that the outputs of the PT are very similar to those of the PV, but more restricted: e.g., hardly any input to the reticular nucleus of the thalamus is observed, the nucleus accumbens is less densely targeted and in the ventral subiculum, fibers are confined to the molecular layer whereas the PV also innervates the pyramidal layer.

3.1.3. Intermediodorsal nucleus

3.1.3.1. Location and morphology. As its name implies, the intermediodorsal nucleus of the thalamus (IMD) is found in between the left and right mediodorsal nuclei. It is not recognised in all species, and is described in most detail in rats [12,68]. In many studies it is considered to be the medial part of the mediodorsal nucleus. However, on the basis of input and output relationships the IMD can be clearly dissociated.

3.1.3.2. Input. Although many retrograde studies describe the input of the midline region of the thalamus on the basis of retrograde tracer injections encompassing various midline structures (e.g., Ref. [27]), very few studies describe

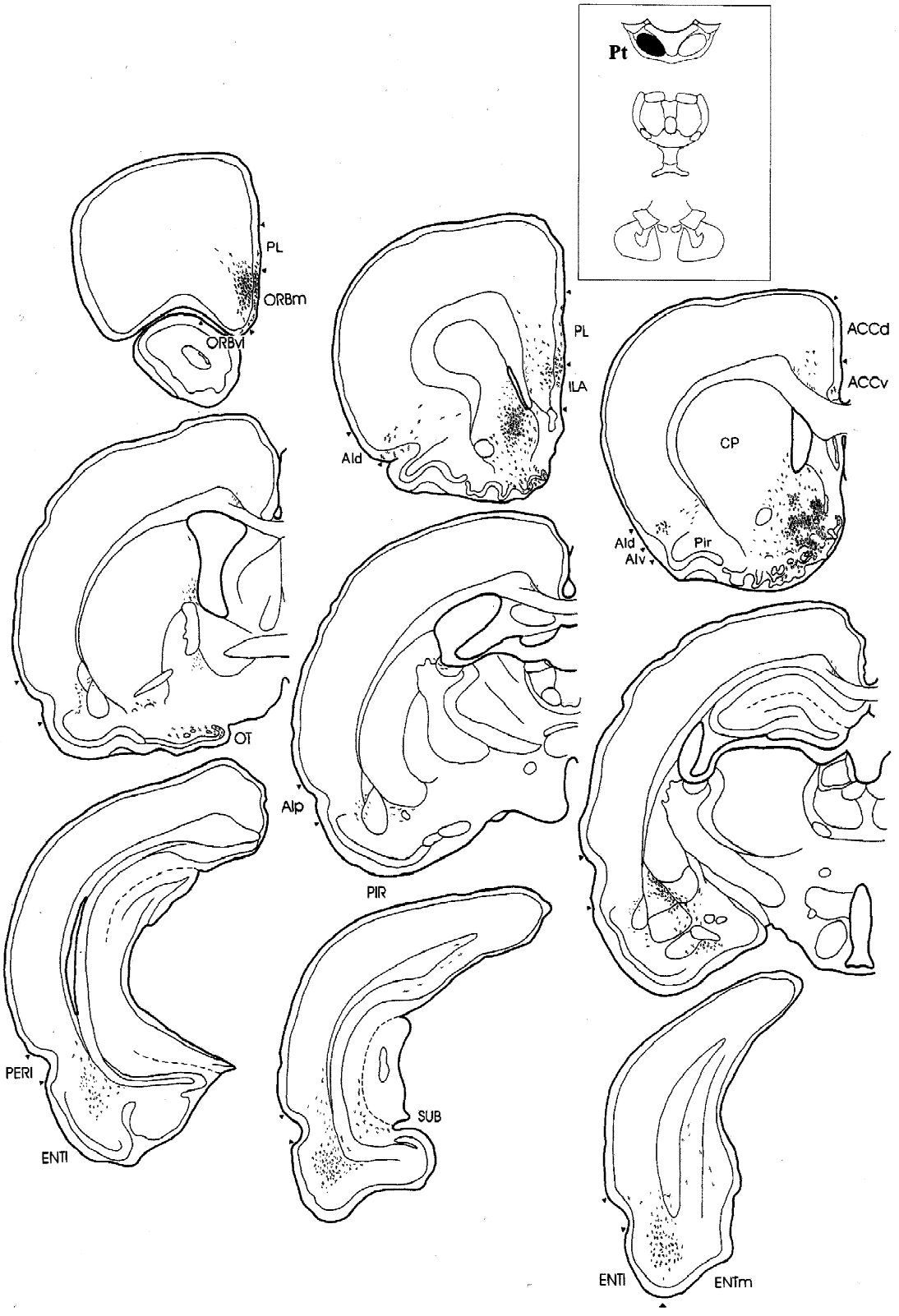

Fig. 3. Overview of the pattern of terminal and passing fiber labeling following a representative injection of the anterograde tracer PHA-L in the parataenial nucleus of the rat thalamus, adapted from Berendse and Groenewegen [13]. For abbreviations see Fig. 2.

the input structures of the IMD in particular. The anterior limbic, but not the rest of medial limbic cortex, sends fibers to the IMD in cats [71]. In addition, Vertes showed that in rats the supramammillary nucleus supplies a significant input to the IMD [157].

We analyzed 27 cases with injections of BDA or PHA-L in the IMD, taken from Wright and Groenewegen [167] and Berendse and Groenewegen [12,13]. Caudal and rostral injections were selected and compared.

3.1.3.3. Trajectory of efferent fibers. The routes taken by the fibers emanating from the IMD are highly comparable for the different cases investigated. Fibers leave the thalamus via the inferior thalamic peduncle, coursing obliquely from the IMD in a straight line ventrolaterally towards the amygdala. This bundle passes through the reticular nucleus of the thalamus. From the reticular nucleus, the fibers course anteriorly and divide into three portions: one bundle runs underneath the anterior forceps of the corpus callosum, supplying the insular cortex; a second component projects directly into the ventral striatum; a third bundle runs on the medial side of the genu of the corpus callosum and projects to the medial prefrontal cortices.

Few fibers can be detected in the cingular bundle towards parahippocampal cortices and a small number of labeled fibers runs via the stria terminalis towards the amygdala.

3.1.3.4. Terminal labeling. Despite differential and non-overlapping tracer deposits in the IMD, no clear topographical differences could be found. The pattern of fiber labeling is illustrated by a single representative case in Fig. 4.

Cerebral cortex The prelimbic and infralimbic cortices receive heavy plexi of terminating fibers in both superficial (I) and deeper layers (III and V). The anterior cingulate cortex is lightly labeled. The medial orbital cortex shows no terminating fiber labeling, but the lateral orbital cortex contains a plexus of labeled fibers that is continuous with a heavy plexus in the agranular insular cortex. The latter plexus is densest in layers I, III and V. The plexus in the insular cortex is continuous caudally with a smaller amount of fibers terminating in the perirhinal cortex. In addition, there is a significant projection to deep layers of the lateral but not the medial entorhinal cortex. No differences could be detected in quality or quantity of terminating fibers arising from injections in the rostral or more caudal part of the IMD.

Subcortical telencephalic structures In all cases, the medial part of the nucleus accumbens receives a moderate amount of fibers throughout the length of the structure. The greatest part of fibers is directed towards the core of the nucleus accumbens and the adjacent part of the ventral caudate putamen and olfactory tubercle. The labeling in the caudate-putamen extends along the entire rostro-caudal extent of the structure. There is a consistent labeling throughout the cases investigated in layer I of the olfactory tubercle. The amygdala in all cases receives a moderate amount of terminating fibers in its basolateral, lateral and central nuclei. Some fibers can be seen to terminate in the claustrum. Again, no differences were noted between the rostral and caudal injections in the IMD.

Diencephalon In some cases, labeling of the mediodorsal nucleus and PV was seen rostral to the injection site. In all instances, a marked labeling in the reticular nucleus was seen, in particular in the ventromedial tip of the most rostral extension of the nucleus.

3.1.3.5. Comparison with previous reports and other species. The IMD has been only seldomly mentioned in tracing studies of the thalamus. Previous studies in rats have obtained results that are comparable to those reported here [145].

In cats, projections from the rhomboid nucleus, which is the equivalent of the rat IMD [12], have been described [9,93,95,120,124]. These findings concord to a great extent with those found here. Thus, similar to our findings, striatal and amygdalar areas are found to be the main target fields [93,95]. In contrast, the slight intrathalamic projections that we report here have, to the best of our knowledge, not been described elsewhere. Thus, our data and those from the literature are in general agreement. The IMD shows a restricted pattern of efferent connections. Its main targets, much like the PV and PT, are the ventral striatum, medial and lateral prefrontal cortex and the amygdala. Like the PV, it projects strongly to the medial part of the rostral reticular nucleus. Unlike the PV and PT, however, a strong projection to the agranular insular cortex is found. Interestingly, despite the length of the nucleus, no topographical organization has been observed in the projection patterns.

3.1.4. Reuniens nucleus

3.1.4.1. Location and morphology. The nucleus reuniens thalami (Re) is located in the anterior one-third of the rat thalamus. Anteriorly, it is divided into a left and right component by the third ventricle, towards its tail the two structures fuse and become a mass of cells in the midline of the thalamus, lying immediately dorsal to the third ventricle. The nucleus consists of a conglomerate of loosely packed cells [68]. At its posterior end the main mass of the Re is bordered by the nucleus perireuniens on both sides.

3.1.4.2. Input. Herkenham produced the first and most complete overview of inputs of the Re, using selective injections of the retrograde tracer horseradish peroxidase in

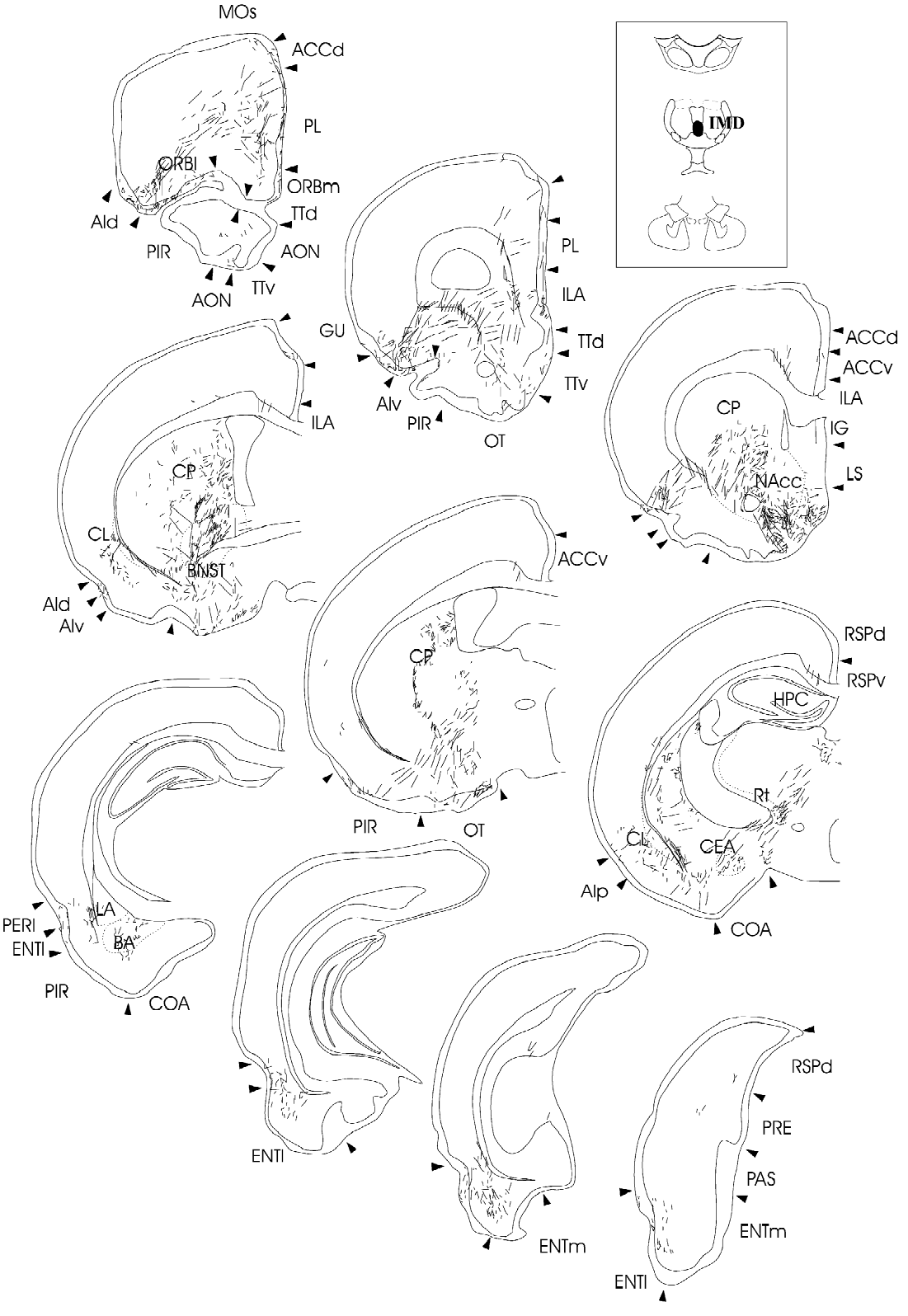

Fig. 4. Overview of the pattern of terminal and passing fiber labeling following a representative injection of the anterograde tracer BDA in the intermediodorsal nucleus of the rat thalamus. For abbreviations see Fig. 2.

rats [55]. Subsequent studies have supplied additional information and have refined Herkenham's findings. Cortical input originates in the deep layers of the infralimbic, prelimbic and perirhinal cortices [32,59,136,163], whereas in cats additional projections from the cingulate cortex, dorsal and ventral retrosplenial cortices and the presubiculum have been noted [71]. There is a topographically organized projection from the subiculum in rats [163,164], which has also been reported in monkeys [1]. Amygdalar input is sparse and originates in the medial and anterior nuclei in the rat [55] and from medial and central nuclei in the monkey [2].

Basal forebrain inputs arise from the nucleus of the diagonal band and the bed nucleus of the stria terminalis. Diencephalic inputs include projections from the reticular nucleus of the thalamus, the lateral geniculate nucleus, the zona incerta, the medial and lateral preoptic area, the medial and lateral hypothalamus, and the premammillary and supramammillary nuclei [115,157]. Brain stem areas projecting to the Re are the ventral tegmental area, dorsolateral tegmental nucleus, the superior colliculus, the central grey, the dorsal, median and central raphé and the parabrachial nucleus [15]. Anterograde tracing studies in rats show a weak input from the nucleus reticularis gigantocellularis [107] and a denser input from the subnucleus reticularis dorsalis and the cuneate nucleus [159].

We analyzed 40 injections of anterograde tracers at different rostrocaudal, dorsoventral and mediolateral sites in the Re and the perireuniens nucleus, in order to study the topographical organization in the output patterns. The injections were obtained from previous studies in our laboratory [12,13,35,165].

3.1.4.3. Trajectory of efferent fibers. As has been described by Wouterlood et al. [165], fibers from the Re follow several pathways to their destinations. The majority of fibers courses laterally towards the medial fourth of the reticular nucleus where the ongoing fibers aggregate in the inferior thalamic peduncle. These fibers course rostrally and turn medialward, dorsal to the anterior commissure, giving off fibers along their way to the piriform cortex, claustrum and olfactory tubercle. The remaining fibers split into two bundles, supplying the rostral and caudal cortical regions, respectively.

3.1.4.4. Terminal labeling. Clear topographic differences were observed after differential placement of tracers in the Re and perireuniens. Representative examples of fiber labeling after a medial injection centered on the rostrocaudal axis of the Re and an injection in the perireuniens are shown in Figs. 5 and 6.

Cerebral cortex Before describing the topographical differences of fiber labeling arising from different injection sites in the Re nucleus and perireuniens, the pattern common to all cases analyzed will be described. Thus, the cortical areas that receive fibers include in all cases the medial frontal cortex. The prelimbic and infralimbic cortices show dense plexi in layers Ia, V and VI. The medial orbital cortex exhibits labeling in layers Ia, III and V. The anterior cingulate cortex is innervated sparsely and the labeling continues very lightly lateralward into the adjacent motor cortex. Caudally, the cingular labeling is continuous with that seen in the dorsal retrosplenial cortex, preferentially in layer I. Layers I, III and V of agranular insular cortex receive fibers. The superficial labeling is continuous with that found in the perirhinal and piriform cortices.

The medial and lateral divisions of the entorhinal cortex show moderate labeling in layers I and III with a few fibers scattered throughout the deeper layers. This labeling becomes more dense towards caudal levels of the entorhinal cortex. Heavy fiber labeling is found in the stratum lacunosum moleculare of the CA1 area of the hippocampus continuing into the molecular layer of the subiculum. The pre-, and parasubiculum receive fibers in their superficial layers.

Both rostrocaudal and mediolateral topographies were found. Caudal injections result in weaker labeling of the same structures than do injections in rostral Re. On the mediolateral axis, however, differential placement of injections shows more qualitative differences of terminations in the target areas. Thus, compared to medial injections, lateral Re and perireuniens injections result in stronger labeling of prelimbic, infralimbic and anterior cingulate cortices, which is more concentrated in layer Ia. Also, in layers III and V of the medial orbital cortex an especially dense plexus can be seen after lateral Re or perireuniens injections. In addition, injections in the nucleus perireuniens result in labeling of fibers preferentially in the ventral subiculum, whereas the fibers originating in the medial Re reach the dorsal and ventral subiculum throughout.

Subcortical telencephalic structures The Re injections result in very sparse fiber labeling in the striatum. A few terminating fibers are visible in the medial caudate putamen, amidst bundles of passing fibers. The amygdala receives sparse labeled fibers in its basal complex. The endopiriform nucleus receives a moderate amount of fibers.

Diencephalon The only subcortical structures that show fiber labeling after injections in the Re are other thalamic midline and intralaminar nuclei (including the paraventricular, rhomboid, central medial and intermediodorsal nuclei) and the mediodorsal nucleus that show a few scattered fibers. The reticular nucleus shows a heavy plexus in its most medial tip, along with the zona incerta. The intrathalamic fiber labeling can be found bilaterally, even if the injection is placed away from the midline. A

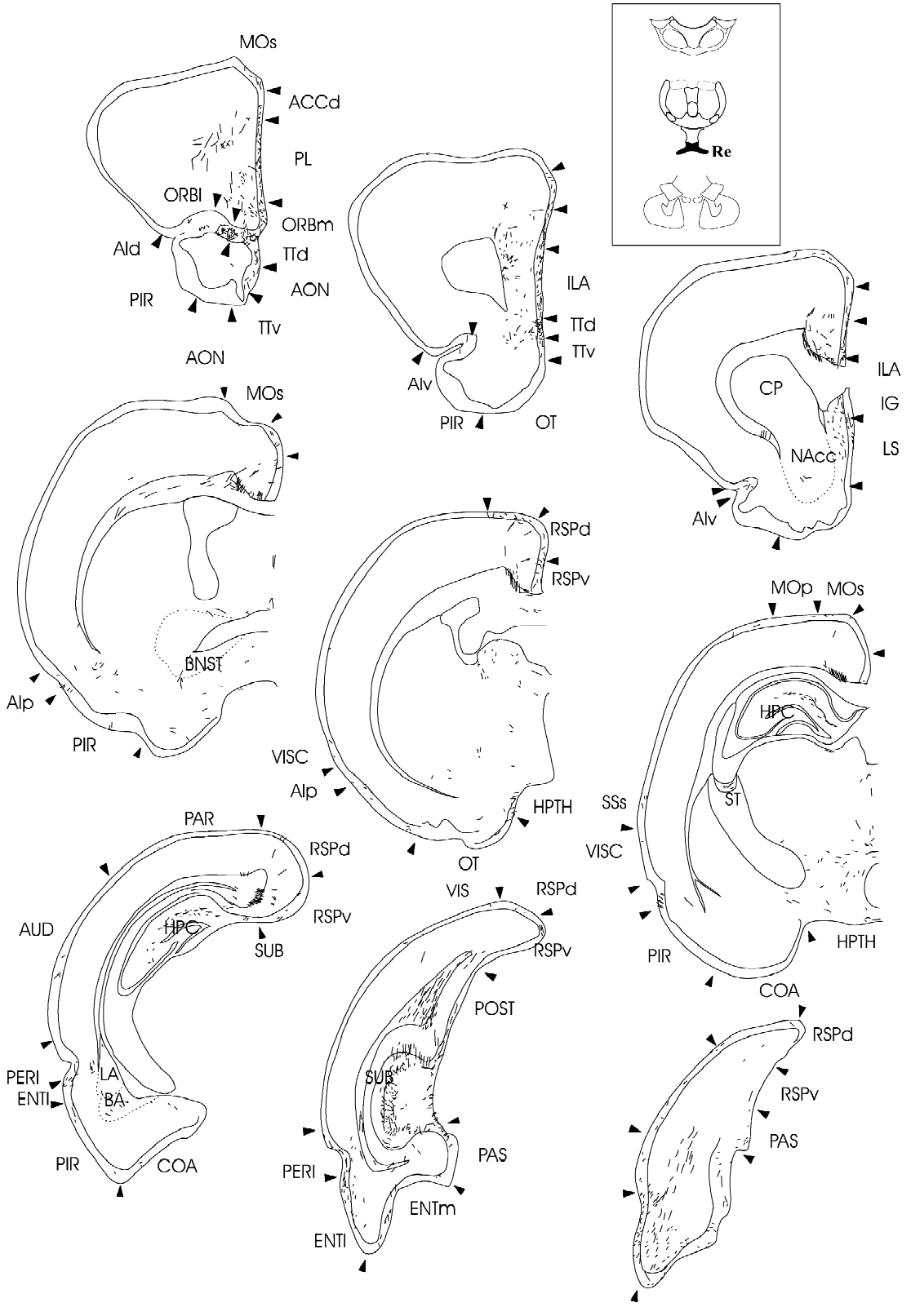

Fig. 5. Overview of the pattern of terminal and passing fiber labeling following injection of the anterograde tracer PHA-L in the medial reuniens nucleus of the rat thalamus, located centrally at the rostrocaudal axis of the nucleus. For abbreviations see Fig. 2.

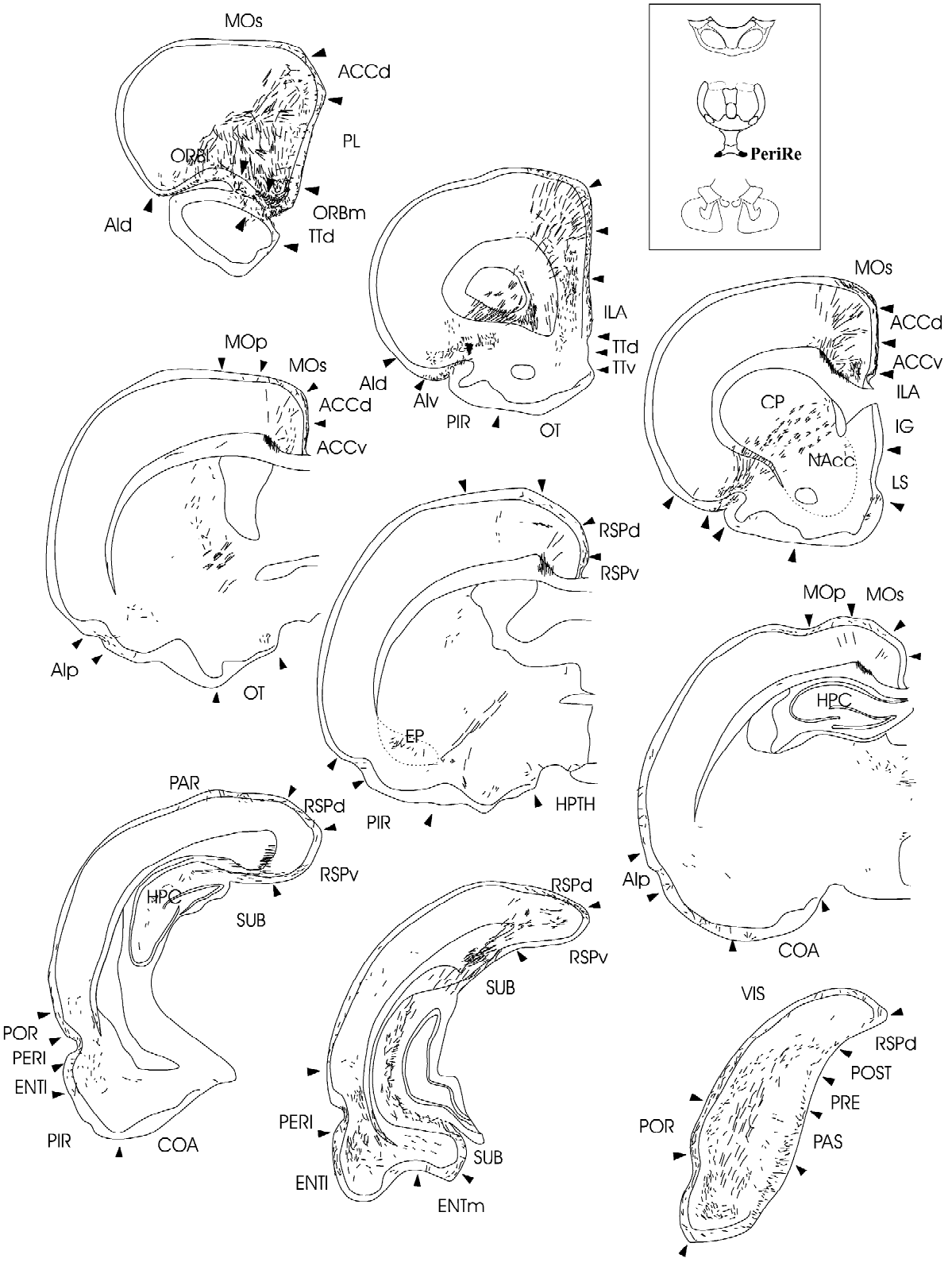

Fig. 6. Overview of the pattern of terminal and passing fiber labeling following injection of the anterograde tracer PHA-L in the perireuniens nucleus of the rat thalamus. For abbreviations see Fig. 2.

few fibers are seen scattered throughout the posterior, arcuate and lateral hypothalamic nuclei.

Brainstem Only in the periaqueductal grey are a few fibers discerned.

3.1.4.5. Comparison with previous reports and other species. The present results concur in general with those obtained by Herkenham [55]. Herkenham did, however, describe more subcortical projections which were not found in this study, such as diffuse projections to the hypothalamus with stronger inputs to the median eminence and suprachiasmatic nucleus, projections to the anterior olfactory nucleus, nucleus accumbens, olfactory tubercle, claustrum, septum, preoptic area, pretectum, superior colliculus, rostral ventral tegmental area and central grey. These differences are possibly due to the lesser specificity of the retrograde HRP method which results in relatively large injection sites. Projection patterns have been shown to be quite constant among different species investigated; the rat [29,40,50,95,96,105,114–116,145,148,168], cat [93,101,124,170] and monkey [3,60]. A few exceptions have been described. Yeterian and Pandya report that in monkeys, the superior temporal sulcus receives afferents from the Re along its entire length [171]. Also, in contrast to the widespread projection to cingulate cortex in rats, in monkeys projections are only found to anterior cingulate cortex, area 24 [160].

Ohtake and Yamada describe efferent fibers to globus pallidus and caudate putamen in rats, in contrast to our data [96]. They also report intrathalamic projections to the anteroventral, ventrolateral, paraventricular, reticular, laterodorsal, central medial, ventromedial, ventroposterior, parafascicular and lateroposterior nuclei. The current study shows a more restricted intrathalamic projection, i.e., to other members of the midline and intralaminar groups of nuclei. This may be explained by larger injection sites in the former study, encompassing structures outside the Re.

Taken together, it may be concluded that the Re projects strongly and consistently across species, to the medial prefrontal and orbital cortices, to the hippocampus including subiculum, pre- and parasubiculum, and to the entorhinal and perirhinal cortices. The cortical projections are much stronger than the projections to subcortical areas, which places the Re in a different position than the midline thalamic nuclei discussed so far.

3.1.5. Rhomboid nucleus

3.1.5.1. Location and morphology. Following Berendse and Groenewegen [12], we locate the nucleus rhomboideus (Rh) beneath the internal medullary lamina. Rostrally, it is confluent with the anteromedial nucleus and consists of a left and a right part with winglike lateral extensions. Towards its caudal part the two structures merge in the midline. The nucleus is easily distinguished by its conspicuous shape and its large and darkly staining cells.

3.1.5.2. Input. Data on inputs to the Rh are sparse and are only available in the rat. Subcortical input to the Rh has been found to arise in the nucleus raphé centralis [15], the nucleus reticularis gigantocellularis [107] and the supramammillary nucleus [157]. All these inputs are weak.

We analyzed two cases with pure injections of the Rh and one with contamination of adjacent structures. Two cases were taken from Berendse and Groenewegen [13], one is a previously unpublished case.

3.1.5.3. Terminal labeling. The small number of cases analyzed here does not allow investigation of topographical differences in patterns of fiber labeling. The patterns of terminating labeled fibers is highly comparable for the three cases investigated. The results are shown in Fig. 7, taken from Berendse and Groenewegen [13].

Cerebral cortex In the three cases examined, widespread fiber labeling in cortical and subcortical areas is found. Terminating labeled fibers are seen in prelimbic and infralimbic cortices, taenia tecta and induseum griseum, ventral and dorsal anterior cingulate cortices, primary and secondary motor cortices, primary and secondary somatosensory cortices, visceral, agranular insular, auditory, gustatory, perirhinal and lateral entorhinal cortices. Some fibers are detected in the hippocampal formation. In all cortical areas, the labeling is found in layer I. In the secondary motor, primary and secondary somatosensory, visceral and gustatory cortex, perirhinal and lateral entorhinal cortices this is accompanied by labeling in layer V.

Subcortical telencephalic structures A consistent but sparse labeling is found in the ventral parts of the caudate-putamen and the ventrolateral part of the shell of the nucleus accumbens. The labeling is diffuse. Scattered fibers are found in the olfactory tubercle.

Diencephalon No labeling of other intralaminar, midline or relay nuclei of the thalamus, nor of the hypothalamus could be found in any of the cases. The reticular nucleus receives fibers in its medial tip at rostral levels.

3.1.5.4. Comparison with previous reports and other species. This pattern of labeling has been largely, but not totally observed by others. Contrary to our finding of preferential labeling in layer I, Ohtake and Yamada report diffuse terminations in layers II–VI in the rat [96]. In addition, they describe modest labeling in the ventrolateral, ventromedial, central medial, ventroposterior, and gelatinose nuclei of the thalamus. In the hypothalamus, the anterior and lateral hypothalamic area are targeted. They further report the zona incerta to be moderately labeled.

Projections to the anterior and posterior cingulate cortices have been described before [40]. Projections to the

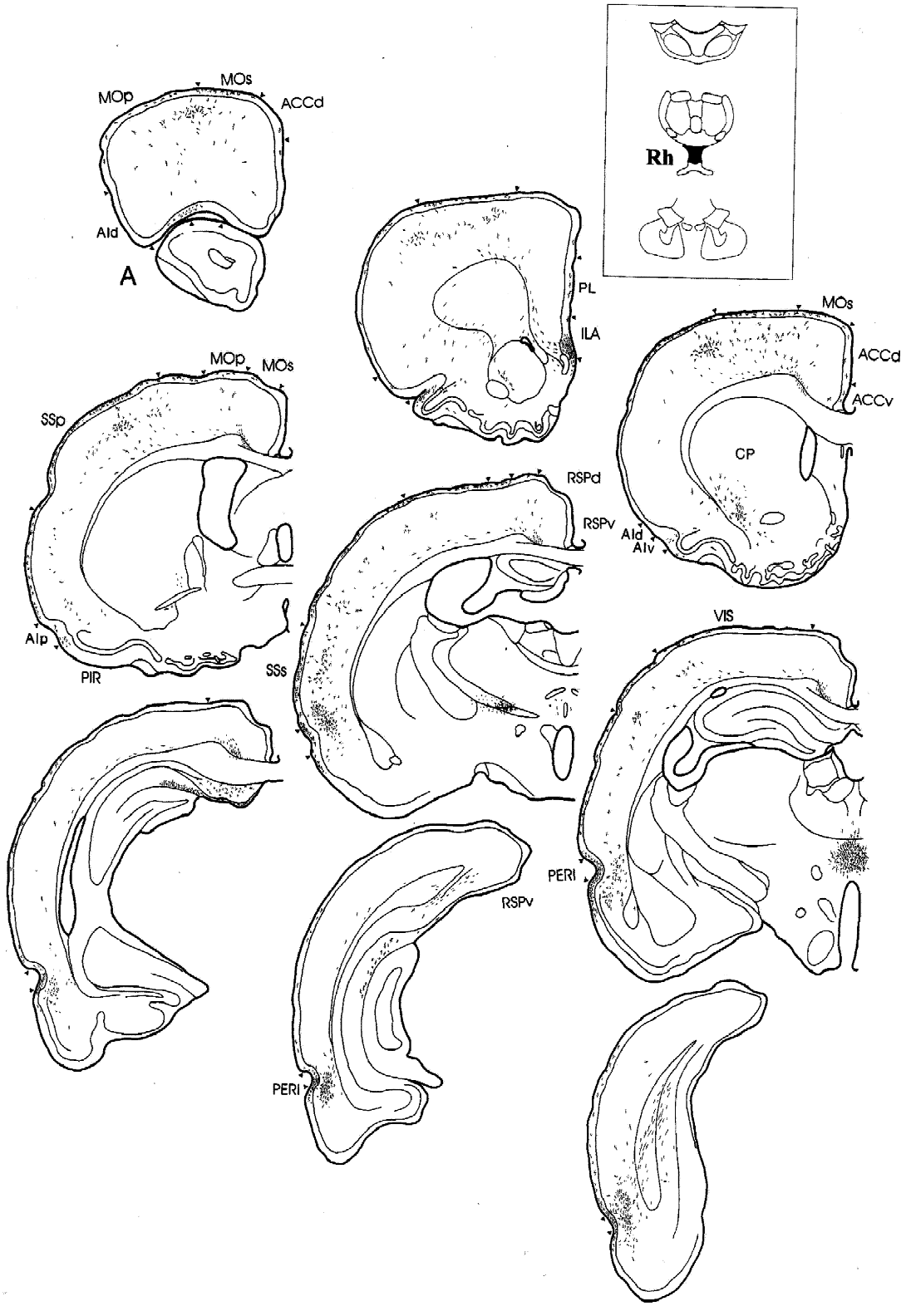

Fig. 7. Overview of the pattern of terminal and passing fiber labeling following a representative injection of the anterograde tracer PHA-L in the rhomboid nucleus of the rat thalamus, adapted from Berendse and Groenewegen [13]. For abbreviations see Fig. 2.

hippocampus proper have also been described by others on the basis of retrograde tracer application in Ammon's horn and the dentate gyrus [114,145]. The bed nucleus of the stria terminalis and the basolateral nucleus of the amygdala have been found to receive some fibers [145]. In cats, Yanagihara et al. report efferents to the pre- and parasubiculum [170]. The inconsistencies between the results of the different studies notwithstanding, the Rh can be said to project to cortical and subcortical areas in a widespread manner without strong preferences for specific areas. In contrast to the other intralaminar and midline nuclei, the projections from Rh are not confined to limbic structures and association cortices, but reach primary and secondary motor and sensory cortices as well.

3.2. Intralaminar nuclei of the thalamus

The intralaminar nuclei are made up of a rostral group, consisting of the central medial, paracentral and central lateral nuclei; and a caudal group, comprising the centre médian and parafascicular nuclei.

3.2.1. Trajectory of efferent fibers of the intralaminar nuclei

The trajectory of fibers is similar for all members of the intralaminar group of nuclei. From the injection site, fibers run towards the reticular nucleus, turn rostrally along the internal capsule and the ventral striatum to the genu of the corpus callosum, where they divide into a bundle in the cingulum and a more loosely arranged group of fibers running along the external capsule supplying the cortical mantle. In addition, some fibers can be seen projecting directly from the ventral thalamic peduncle into the target area and some passing fibers are found in the superficial layers of the insular and perirhinal cortices.

3.2.2. Rostral group

3.2.2.1. Location and morphology. This nucleus is easily identifiable in all species as a centrally located group of large, deeply staining and flattened cells clearly distinct from the midline nuclei lying dorsal and ventral to it. Laterally, however, the nucleus is continuous with the paracentral nucleus on both sides. In mammals with a fused midline, the left and right nuclei form a single, centrally positioned nucleus.

3.2.2.2. Input. The main sources of input to the central medial (CeM) nucleus seem to be subcortical structures. These include the reticular formation [107,158], serotonergic cell groups [156], the supramammillary nuclei [157], the cholinergic pedunculopontine and laterodorsal tegmental nucleus [51], deep cerebellar nuclei such as the dentate, fastigial and posterior interpositus nuclei [52], and superior colliculus [169]. In general, these areas give rise to sparsely distributed terminals in the CeM. In rats, cortical input from the anterior cingulate cortex has also been found (B.F. Jones and M.P. Witter, unpublished data).

In cats, cortical input has been described from the anterior limbic, dorsal retrosplenial and presubicular areas, with the latter two supplying fibers from both the ipsilateral and contralateral side [71].

We analyzed six injections in the CeM of the rat, taken from the work of Berendse and Groenewegen [12,13]. Additionally, we prepared four cases with injections aimed specifically at the caudal part of the nucleus. Together, the injections therefore covered the entire length of the nucleus, enabling the analysis of possible topographies in terminal fiber labeling.

3.2.2.3. Terminal labeling. There is a striking difference in the pattern of terminal labeling following rostral or caudal injections in the CeM. At cortical levels, virtually no overlap can be seen between the termination fields resulting from either rostral or caudal injections. Examples of the fiber labeling following a rostral or a caudal tracer substance placement is shown in Figs. 8 and 9.

Cerebral cortex The rostral injections result in a marked labeling of layers I, III and V of ventral and dorsal subdivisions of the anterior cingulate cortex with no labeling of adjacent areas. Further caudally, in the retrosplenial cortex, only a few scattered fibers are observed in its ventral part. Sparse labeling is found in the deep layers of the lateral entorhinal cortex.

The caudal injections on the other hand, do not result in labeling of the cingulate cortex. Instead, fibers can be found in layers I, III and V of primary motor, gustatory,visceral, and primary somatosensory cortices. A few fibers are observed in perirhinal and lateral entorhinal cortices.

Subcortical telencephalic structures Rostral injections result in heavy labeling of the most medial part of the caudate putamen and the adjacent part of the nucleus accumbens, most pronounced in the core. This labeling is found throughout the rostral-caudal extent of the striatum. Rostral injections label the basolateral and, more strongly, the basomedial nucleus of the amygdala. Sparse labeling is observed in the claustrum.

Caudal injections in the CeM produce labeling in ventrolateral caudate putamen (i.e., the fundus striatum) but not in the nucleus accumbens. The labeling in the fundus striatum is continuous with labeling of the central nucleus of the amygdala. A few scattered fibers are found in the lateral nucleus of the amygdala.

Diencephalon Both rostral and caudal injections give rise to terminating fibers in the reticular nucleus, slightly more lateral than in the case of the other midline and intralaminar nuclei (not illustrated). Interestingly, the caudal injections produce a marked intrathalamic fiber labeling of both passing and terminating fibers. This fiber

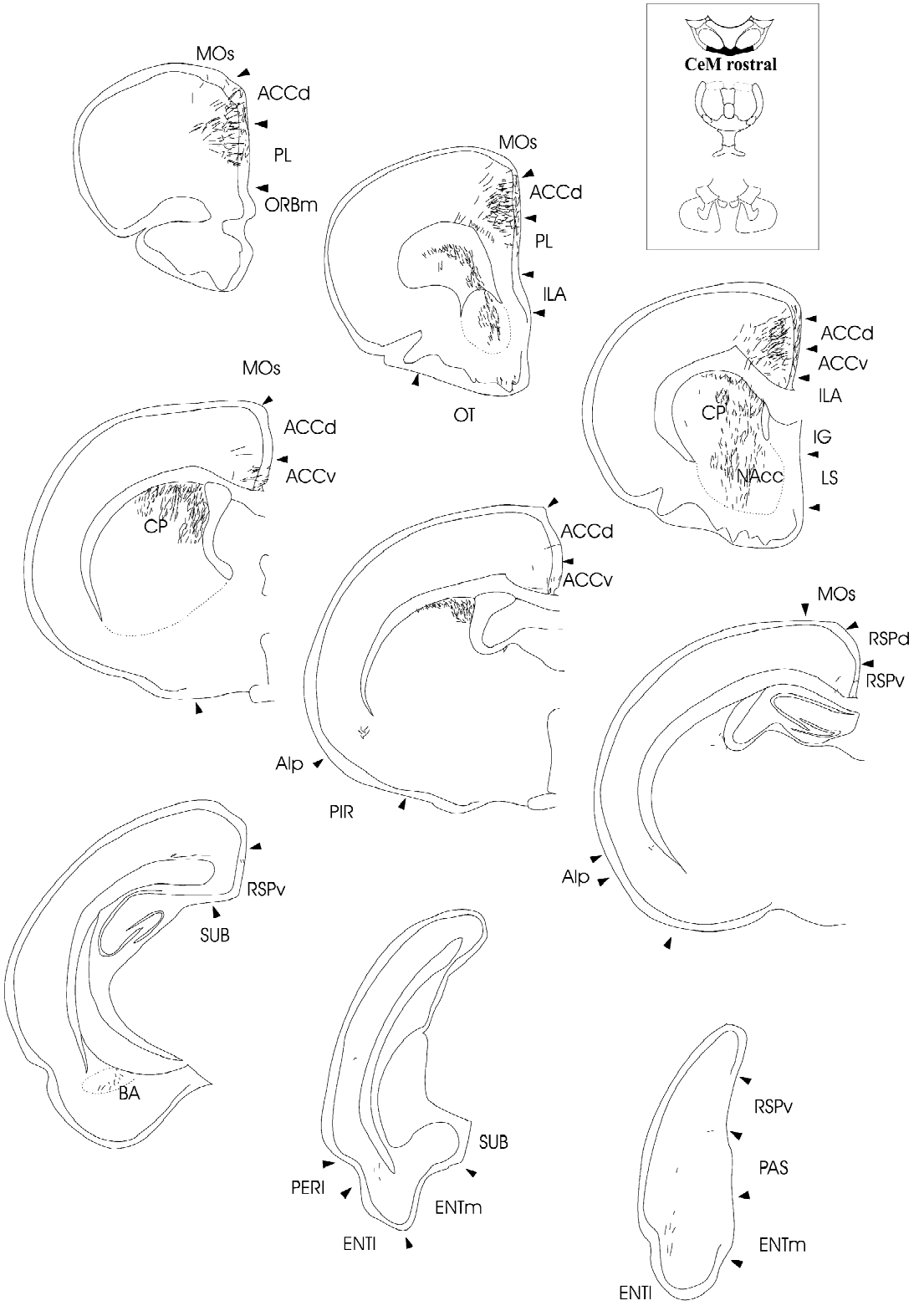

Fig. 8. Overview of the pattern of terminal and passing fiber labeling following injection of the anterograde tracer PHA-L in the rostral part of the central medial nucleus of the rat thalamus. For abbreviations see Fig. 2.

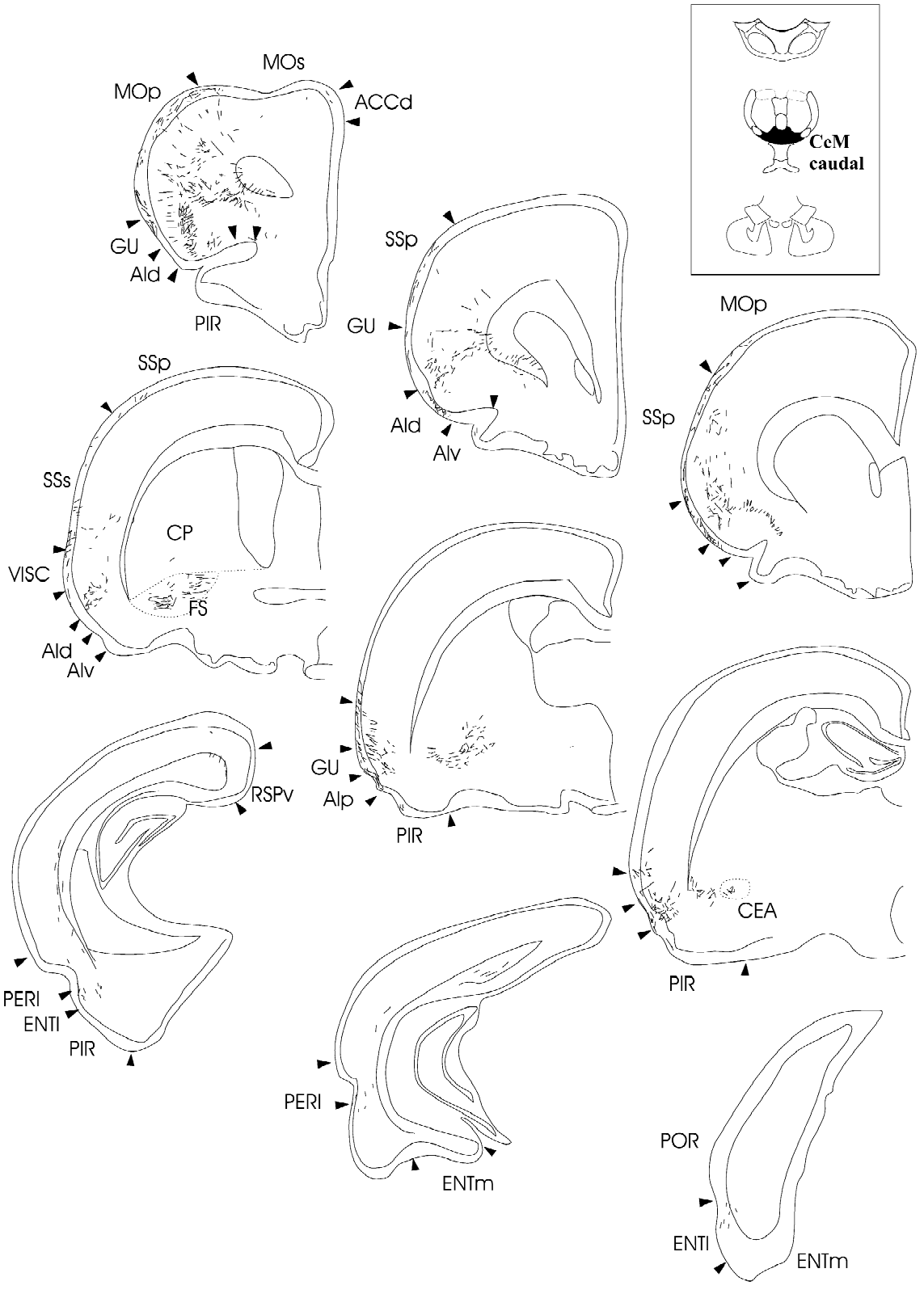

Fig. 9. Overview of the pattern of terminal and passing fiber labeling following injection of the anterograde tracer BDA in the caudal part of the central medial nucleus of the rat thalamus. For abbreviations see Fig. 2.

labeling is confined mostly to the midline structures such as the Re and Rh, but also the ventromedial nucleus receives terminating fibers. When caudal injections are placed in the lateral extension of the CeM, a strong contralateral intrathalamic terminal labeling at the homologous site is seen (not shown).

Judged by the patterns of terminating fibers, the caudal CeM seems to have more in common with the Rhomboid nucleus than with the anterior CeM. This cannot be explained by contamination of the injection site with the Rhomboid nucleus since the caudal injections stay well clear of the latter.

3.2.2.4. Comparison with previous reports and other species. The projections to the medial limbic, or anterior and posterior cingulate cortices, have been described by several authors for the rat [21,67,148,150], cat [82,93,95,116] and monkey [160]. Some authors describe terminals reaching the perirhinal cortex in the rat [50], the entorhinal cortex in the monkey [60], and the entorhinal cortex and visual cortices in the cat [73,170]. Herkenham [56] reported widespread cortical projections of the CeM in rats, rather than the restricted patterns of projections described here and by others. These contrasting results might be due to the involvement of the rhomboid nucleus in the injections made by Herkenham.

Projections to the caudate-putamen and amygdala, similar to those reported here, have been described by other authors for the rat [21,67,145,149] and cat [9,64,120,124].

The striking differences between the patterns of projections arising from the rostral and caudal parts of the CeM have to our knowledge not been described before. Only in a study of the hamster, it was described that the caudal part of the CeM and not the rostral part projects to the agranular insular cortex [112]. This concurs with the current findings in rats.

3.2.3. Rostral group: paracentral nucleus

3.2.3.1. Location and morphology. The paracentral nucleus (PC) is a thin strip of cells that is continuous with the CeM medially, and the central lateral nucleus laterally. Its cells are difficult to distinguish from those of the latter, but appear more flattened. The PC lies in the anterior and middle portion of the IML, intercalated between the mediodorsal and the ventral nuclei. Towards its posterior end, its place is taken by the larger central lateral nucleus.

3.2.3.2. Input. The structures giving rise to afferents of the PC are, as with most of the midline and intralaminar nuclei, largely of subcortical nature. In rats, projections from the superior colliculus, supramammillary nucleus and reticular formation have been described [107,156, 158,159,169].

In cats, inputs from several nuclei of the pretectum, superior colliculus, ventral and lateral periaqueductal grey, brainstem reticular formation, substantia nigra, locus coeruleus, medial vestibular, entopeduncular and habenular nuclei, zona incerta and the nucleus prepositus hypoglossi have been described. In addition, several intrathalamic sources of afferents were noted: the lateral geniculate, reticular, pulvinar, central medial, parafascicular, ventrolateral, ventromedial and anteroventral medial nuclei [74].

Cortical inputs have been described from the anterior cingulate, retrosplenial, parietal, supplementary motor, somatosensory, and auditory cortices in the cat [71,74] and raccoon [130]. All cortical inputs are of low to moderate intensity. Weak inputs arise from visual cortices but not from the primary and secondary somatosensory cortices [74]. In rats, we have also observed an input from the anterior part of the anterior cingulate cortex (B.F. Jones and M.P. Witter, unpublished data).

We obtained two animals with injections of anterograde tracers in the PC and an additional three with injections that showed contamination with adjacent structures. These were taken from published and unpublished cases prepared in our laboratory by Berendse and Groenewegen [12,13].

3.2.3.3. Terminal labeling. A representative case is illustrated in Fig. 10.

Cerebral cortex In all cases, injections in the PC result in fiber labeling in visual cortices except the primary visual cortex, frontal eye field, anterior cingulate, auditory, and parietal cortices. The plexus in the dorsal anterior cingulate cortex spreads into the adjacent secondary motor cortex. Weak fiber labeling is seen in the posterior agranular insular and perirhinal cortices. Some topographical specificity is apparent, in that the caudal part of PC but not its rostral part sends fibers to the agranular insular and lateral orbital cortices.

Subcortical telencephalic structures The majority of labeled fibers after injections in the PC is found in the striatum. Dense terminal labeling in the caudate-putamen is found. The core of the nucleus accumbens shows a plexus, which extends more lightly into the shell of the nucleus accumbens and the olfactory tubercle. The terminal labeling in the striatum shows a dorsal-to-ventral and a rostral-to-caudal shift, corresponding with a rostral-to-caudal shift of tracer placement in the PC. In all cases, a few fibers are scattered in the amygdala and the claustrum.

Diencephalon The reticular thalamic nucleus receives fibers in its ventromedial tip. No labeling is observed in other thalamic nuclei, or in the hypothalamus.

3.2.3.4. Comparison with previous reports and other species. Many studies (cited below) have described the strong projections to the striatum, including the caudate-putamen and the nucleus accumbens; similarly, the relatively sparse labeling of the cortex has been reported. This

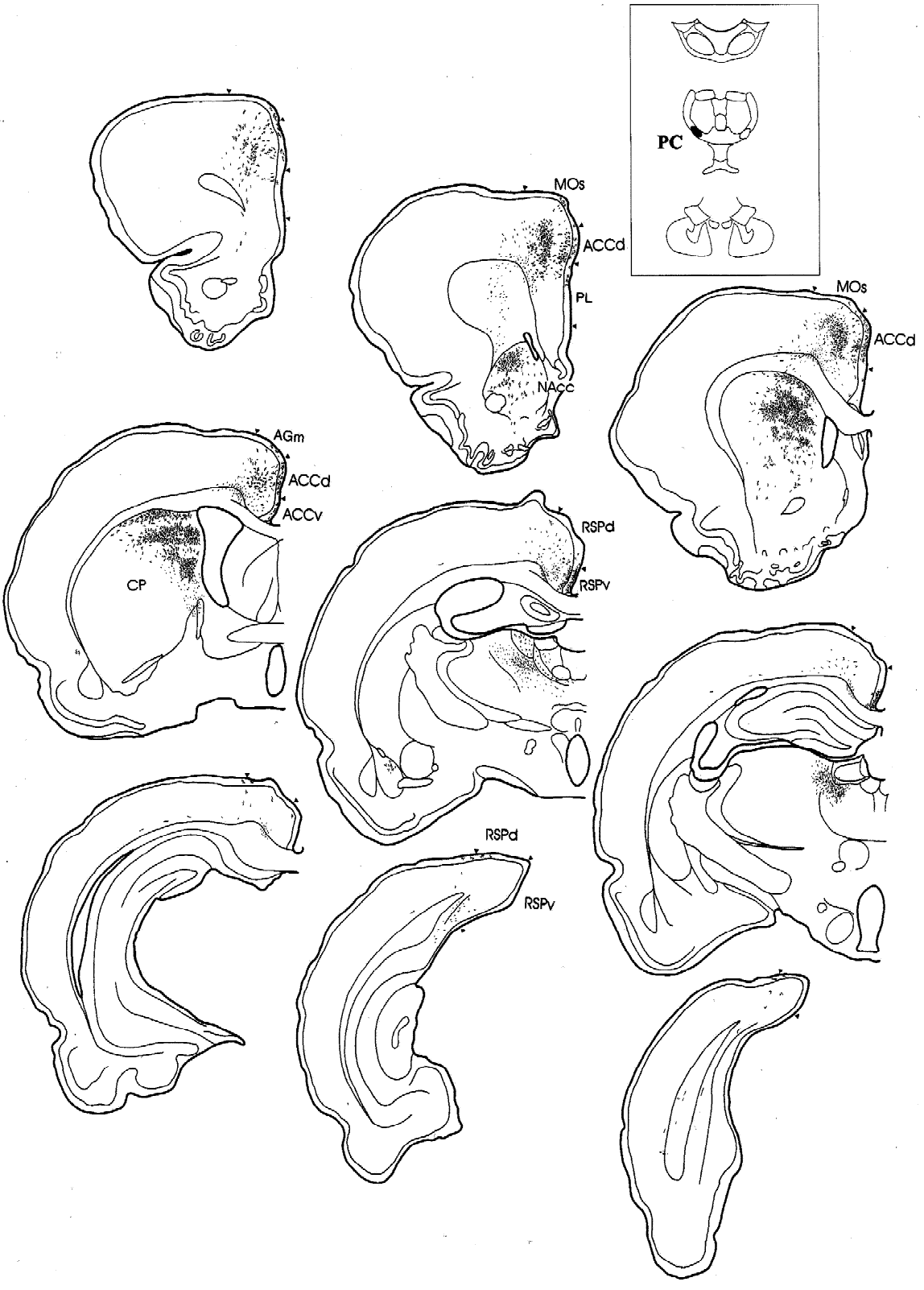

Fig. 10. Overview of the pattern of terminal and passing fiber labeling following a representative injection of the anterograde tracer PHA-L in the paracentral nucleus of the rat thalamus, adapted from Berendse and Groenewegen [13]. For abbreviations see Fig. 2.

cortical projection in all reports is described to show a preference for the anterior and posterior cingulate cortices, and the perirhinal and entorhinal cortices in the rat [10,67,148], cat [9,73,82,95,120,170] and monkey [160]. In the monkey, a projection towards temporal cortex has been shown that is not found in other species [5]. In general, though, the results concur closely with those shown in the current manuscript, regardless of species.

3.2.4. Rostral group: central lateral nucleus

3.2.4.1. Location and morphology. This most dorsal component of the intralaminar nuclei is located posteriorly and dorsally to the paracentral nucleus, and is confluent with it. The central lateral nucleus (CL) is larger than its intralaminar neighbor, but shares many of its connectional characteristics. Hence, the paracentral and central lateral nuclei are often regarded in unison.

3.2.4.2. Input. The CL receives a denser brainstem input than its intralaminar fellow nuclei, as has been described for the rat [51,107,156–159,169] and dog [129]. The mesencephalic, pontine and medullary reticular formation supply afferent fibers, as well as the median and dorsal raphé nuclei, tegmental and pretectal regions, medial and lateral supramammillary nuclei, substantia nigra pars reticulata and superior colliculus. Relatively weaker inputs arise from the periaqueductal grey and locus coeruleus. Afferents from cerebellar nuclei have also been noted in the rat [52] and dog [128]. The cerebral cortex on the other hand provides moderate to light inputs; anterior limbic, anterior cingulate, dorsal retrosplenial cortices are sources observed by Kaitz and Robertson [71] and Kaufman and Rosenquist [74]. In addition, the latter authors note diverse inputs from visual cortices except the primary and secondary visual cortices, and from primary and secondary somatosensory, insular, and auditory cortices. The inputs to the parietal supplementary motor have been described to be bilateral in the raccoon [130]. In addition, we have observed inputs from the anterior and posterior cingulate cortices in rats (B.F. Jones and M.P. Witter, unpublished observations).

We studied eight cases with anterograde tracer injections centered at the CL, derived in part from previous studies [12,13] and in part from new experiments.

3.2.4.3. Terminal labeling. Unless specifically indicated, the distribution of labeled fibers in the different cases is similar. A representative case is shown in Fig. 11.

Cerebral cortex Fiber labeling resulting from injections in the CL is comparable in overall distribution to that seen after injections in the other anterior intralaminar nuclei (the paracentral and central medial nuclei). The area most densely labeled is the dorsal anterior cingulate cortex that shows fibers in layers I, III and V. The labeling continues laterally into the adjacent secondary motor cortex and caudally into the dorsal part of the posterior cingulate cortex. Fibers in anterior cingulate cortex are found more dorsally and the labeling into posterior cingulate cortex extends further caudally following injections in CL, when compared to labeling resulting from injections in PC and CeM. Furthermore, labeling is found in the visual and somatosensory cortices.

Subcortical telencephalic structures The caudate-putamen receives most of the fibers emanating from CL, with the dorsolateral portion being the preferential site of labeling. The projections to the caudate-putamen are topographically organized such that a rostro-caudal gradient in the CL corresponds to a rostro-caudal distribution of terminating fibers in the caudate-putamen. Very few fibers are detected in the core of the nucleus accumbens, no fibers are observed in the amygdala.

Diencephalon The reticular nucleus contains labeled fibers in its ventromedial tip (not illustrated). No labeling is found in other thalamic structures.

3.2.4.4. Comparison with previous reports and other species. In accordance with the current findings, other studies agree that the main target of the CL is the striatum in both the rat and cat [9,10,21,64,67,120], and that the preferential cortical target is the anterior cingulate and, to a lesser extent, the posterior cingulate cortex in rat, cat and monkey [116,120,148,150,160]. In the cat, a weak innervation of the occipital, parietal, temporal and motor and orbital prefrontal cortices has been described [10,74,82,95,170]. Additionally, in the monkey a projection towards the superior temporal sulcus has been noted and a weak projection to the frontal eye field [132,159].

3.2.5. Caudal group

The caudal intralaminar nuclei include the centre médian nucleus (CM) and the parafascicular (Pf) nucleus. In primates these can be reliably separated, in rodents however, they appear a single cell mass and are frequently mentioned under the same header: the parafascicular nucleus. The lateral part of the rat parafascicular nucleus is considered to be equivalent to the centre médian nucleus, whereas the medial part of the rat parafascicular nucleus is homologous to the primate parafascicular nucleus [68]. In the following, the patterns of projections obtained in our injected cases will be described together and the differences between the medial and lateral part will be discussed on the basis of the literature on different species. To avoid confusion, we use the phrase ‘caudal intralaminar nucleus’ when referring to the rat and ‘Pf’ and ‘CM’ when discussing species larger than rodents.

We analyzed four injections centered at the caudal intralaminar nucleus in the rat, two of which were located in the lateral part and two in the medial part of the nucleus. The cases were obtained from the studies of Berendse and Groenewegen [12,13].

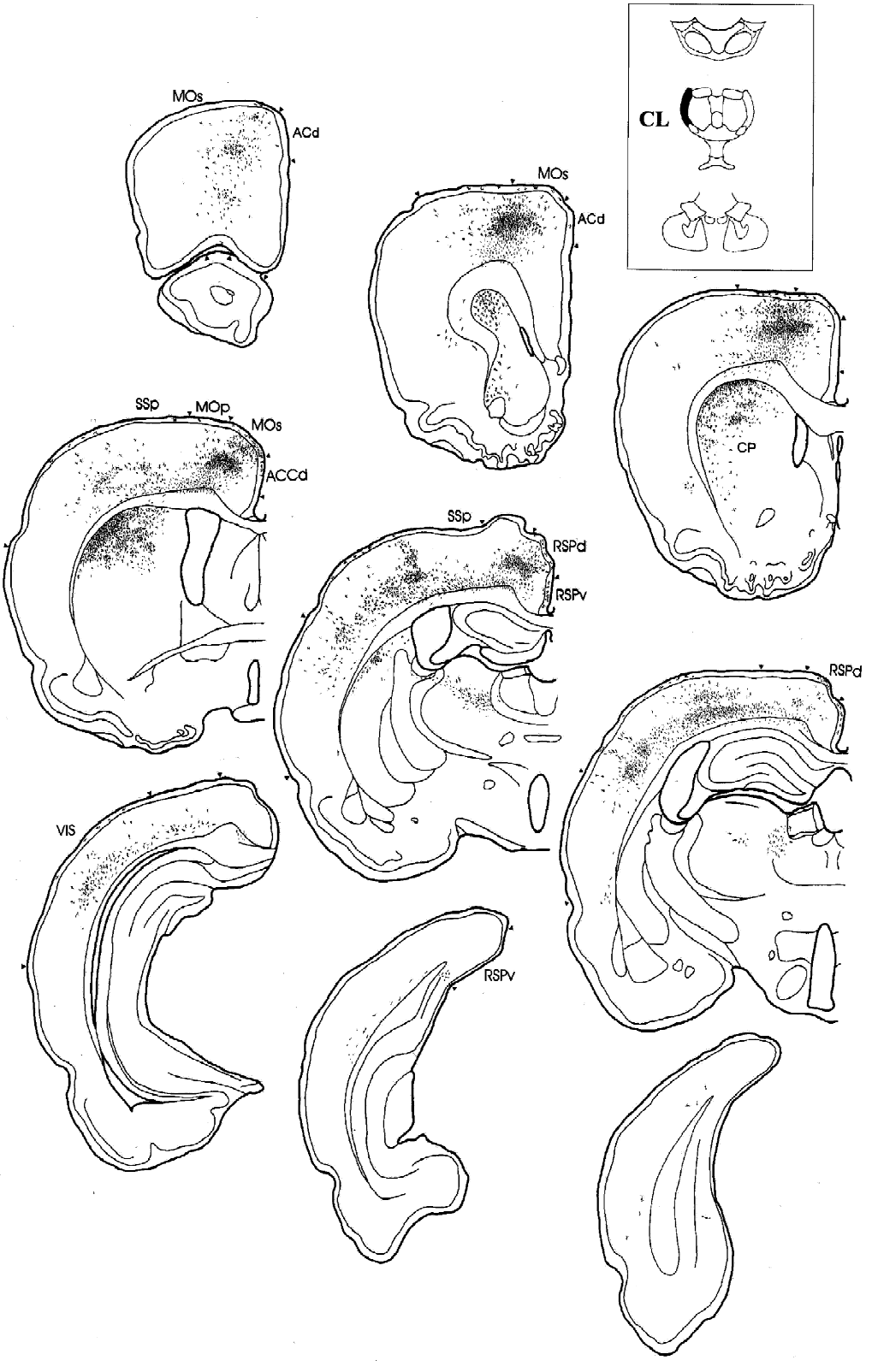

Fig. 11. Overview of the pattern of terminal and passing fiber labeling following a representative injection of the anterograde tracer PHA-L in the central lateral nucleus of the rat thalamus, adapted from Berendse and Groenewegen [13]. For abbreviations see Fig. 2.

3.2.5.1. Location and morphology. The caudal intralaminar nucleus in rats is a large round mass of cells occupying the medial part of the thalamus on each side. Its lateral part contains loosely packed cells that are more darkly stained than those of the medial part. Ventrally it rests almost directly upon the mesencephalon, dorsally it is bordered by the CL nucleus and the lateral and medial habenula. The nucleus lies in close proximity to the fasciculus retroflexus and lateral to the most rostral extension of the periaqueductal grey matter.

3.2.5.2. Input. Many studies have reported subcortical and cortical inputs to the caudal intralaminar nucleus of the rat [15,24,26,52,59,107,122,156–158,169] and cat [25,118,119]. Sources of afferent fibers comprise the spinal cord, medullary, pontine and mesencephalic reticular formation (including the locus coeruleus and raphé nuclei, most densely the dorsal raphé), brainstem nuclei such as the vestibular, parabrachial, tegmental, solitary tract and ambiguus nuclei. There is a projection from the deep cerebellar nuclei and the medial, inferior and superior vestibular nuclei in the rat [52,137] and dog [128]. Furthermore, the reticular nucleus of the thalamus, substantia nigra pars reticulata, zona incerta, pretectum, supramammillary nuclei and the caudate-putamen have been shown to supply fibers in the monkey [104]. Cortical input is derived from layers V and, to a lesser extent, layer VI of frontal and parietal areas in the rat [26], cat [118,119] and monkey [6].

3.2.5.3. Terminal labeling. The labeling after an injection in the lateral part of the caudal intralaminar nucleus is illustrated in Fig. 12.

Cerebral cortex Injections in the lateral part of the caudal intralaminar nucleus lead to widespread labeling of terminating fibers in the dorsal and lateral frontal cortices and parietal cortex. The areas receiving fibers include the primary and secondary motor, and primary somatosensory cortices. In all these areas moderate and diffusely distributed labeling is observed in layers I and IV–VI. The density of fiber labeling tapers off towards more caudal areas.

The distribution of fibers resulting from a medial injection is more restricted and sparser than that of the lateral injections. Sparse fibers are labeled only in the dorsal prelimbic, cingulate, medial agranular and parahippocampal cortices.

Subcortical telencephalic structures The injections in the caudal intralaminar nucleus give rise to an abundance of terminating fibers in the striatum. The density of fiber labeling and the area in the striatum covered is greater than after injections in the midline and rostral intralaminar nuclei. Injections in the lateral part of the caudal intralaminar nucleus result in labeled fibers in the lateral part of the caudate-putamen (Fig. 12). The medial injections produce a complementary pattern of labeled fibers, in reaching the ventromedial caudate putamen and the dorsolateral part of the core of the nucleus accumbens (not illustrated). No fibers are observed in the amygdala.

Diencephalon Fibers are observed rostrally in the reticular thalamic nucleus.

3.2.5.4. Comparison with previous reports and other species. The findings of projections from the caudal intralaminar nucleus in rats are largely in concordance with those described above. The nucleus is the main source of thalamic input to the caudate-putamen and nucleus accumbens [9,21,30,31,39,64,67]. In contrast to the heavy projection to the striatum, the cortical projections are sparse [10,150]. This pattern of projection is seen regardless of the species studied: in species in which the CM and Pf are differentiated, the two nuclei together supply the heaviest thalamic input to the striatum with a relatively weak projection to the cortex, as seen in the cat [64,93,120,121,170], squirrel monkey [125–127] and rhesus monkey [6,67,160].

In addition, in squirrel monkeys the CM has been shown to project to the internal and external segments of the globus pallidus, the nucleus of the solitary tract, substantia nigra pars reticulata and pars lateralis. A few intrathalamic projections have been noted: the ventral thalamus, rostral intralaminar nuclei and caudal reticular nucleus receive input from the CM [126]. In rhesus monkeys, the CM sends fibers to the precentral gyrus [6].

Additional targets of the Pf include the nucleus basalis of Meynert, the subthalamic nucleus, the midbrain and hindbrain reticular formation, the nucleus of the solitary tract and the inferior olive [39,108]. In squirrel monkeys, the Pf projects to targets in the basal ganglia, such as the external and internal globus pallidus and peripallidal area, olfactory tubercle, the substantia nigra pars compacta and ventral tegmental area. Diencephalic targets include the ventral thalamus, rostral intralaminar nuclei, mediodorsal thalamic nucleus and midline thalamic nuclei, as well as the hypothalamus and substantia innominata [126]. In cats, intrathalamic and amygdalar projections have been observed from the Pf [101,121].

In conclusion, the projections from the CM and Pf predominantly reach the striatum and the two nuclei show a topographic complementarity in these projections. Cortical and other projections are scarce. There are a few species differences in the patterns of projections from these nuclei, but the overall pattern is similar to a great extent.

4. Overview of anatomical data

4.1. A proposed clustering into groups on the basis of input/output homogeneities

The experimental data of the output relationships of the intralaminar and midline nuclei of the thalamus described

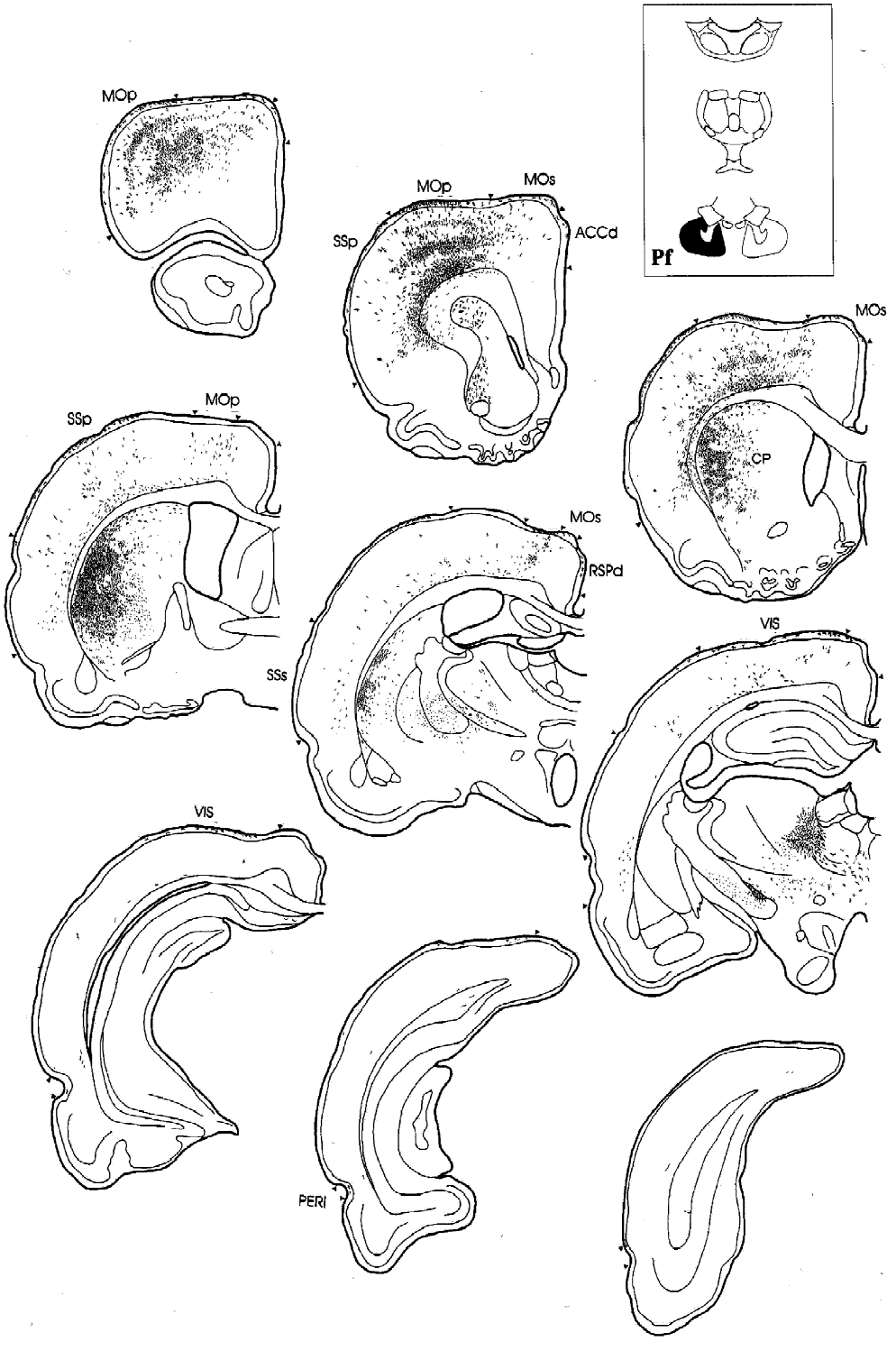

Fig. 12. Overview of the pattern of terminal and passing fiber labeling following an injection of the anterograde tracer PHA-L in the lateral part of the caudal intralaminar nucleus of the rat thalamus, adapted from Berendse and Groenewegen [13]. For abbreviations see Fig. 2.

in this manuscript are based on results obtained in rats. We have further summarized the anatomical data on both input and output connectivity from various mammals, including rats, cats and monkeys, and argue that all species show very similar patterns of connectivity. In accord with this, the equivalence of the various intralaminar and midline nuclei between humans, non-human primates and non-primate mammals has come to be accepted in the literature [68,69,92,141]. The fact that the anatomical data appear to be remarkably similar regardless of the species studied, makes it possible to extrapolate to the human situation. This allows for the anatomical data reviewed here to be discussed in relation to data acquired from human imaging and from clinical studies.

In general, it can be said that the differences in patterns of projection from separate regions within a nucleus are smaller than the differences in the projection patterns between nuclei. Nevertheless, some midline nuclei show a topography in the distribution of fibers, indicating subtle differences in function for separate regions of the nucleus. This is true for the reuniens vs. perireuniens nucleus; the ventral vs. dorsal paraventricular nucleus; the rostral vs. caudal paracentral nucleus. One nucleus shows rather more dramatic topographical differences: the rostral and caudal parts of the central medial nucleus project to mutually exclusive target areas. The difference is such, that the rostral part resembles the other anterior intralaminar nuclei, the central lateral and paracentral nuclei, in terms of projection patterns, whereas the caudal part has more in common with the rhomboid nucleus.

Visual inspection of the patterns of projection indicates that the anatomical relationships of the individual nuclei described in this article appear to cluster together in different groups. This can be appreciated more clearly from the abstract representation of the efferent projections of the midline and intralaminar nuclei in Fig. 13. Based on the similarities in patterns of efference, we propose the following parcellation of the midline and intralaminar nuclei into four groups.

The dorsal group consists of the paraventricular, parataenial and intermediodorsal nuclei. Their main output is directed towards the ventral striatum, especially the medial shell of the nucleus accumbens, the pre- and infralimbic cortices and the amygdala.

The lateral group is constituted by the paracentral, central lateral and anterior central medial nuclei. Fibers emanate towards the dorsal striatum and the cingulate cortex.

The ventral group is made up of the reuniens, rhomboid and posterior central medial nuclei. In contrast to the other intralaminar and midline nuclei, these nuclei send few fibers towards the striatum. Instead, they project to superficial and deep layers of most cortical areas. This ventral group of nuclei projects strongly to non-limbic regions, e.g., gustatory, visceral, insular, auditory and motor cortices. Also, the reuniens nucleus and possibly the rhomboid nucleus project to the hippocampus proper.

The posterior group consists of the centre médian and parafascicular nuclei. The output is mainly directed towards the striatum, but fibers also reach the sensory and motor cortices.

This clustering of individual midline and intralaminar nuclei is based on the projection patterns described above. The similarities between the members of a group suggest that they are involved in the same or closely related functions. On the other hand, the anatomical differences between the groups hint towards a functional differentiation. There is good evidence that the role of these groups of nuclei lies in the domain of arousal and awareness, and that separate roles within this domain for each of the four groups can be outlined. In the following an overview of functional data is given regarding the functions of the four groups of intralaminar and midline nuclei.

4.2. Dorsal group-viscerolimbic: awareness of viscerosensory stimuli

The distinctive features of the members of this group, separating them from the other midline and intralaminar nuclei is that they direct their output towards the medial nucleus accumbens and amygdala [90,149]. Of all four groups, the reciprocal connections with the medial prefrontal cortex are the strongest in this group [59,71]. The group shares with the other three outputs towards agranular insular, and entorhinal cortices. Of the nuclei in this dorsal group, the paraventricular nucleus is the most conspicuous member and it has received the greatest attention over the years. This nucleus stands out among the thalamic nuclei because of its heavy monoaminergic inputs, including histaminergic, adrenergic, noradrenergic, dopaminergic and serotonergic fibers [27,98,103,113]. In addition, it receives fibers carrying the gas neurotransmitter nitric oxide [98]. These diffuse regulatory inputs have led researchers to speculate that the paraventricular nucleus is involved in state-setting properties; an example of the type of situation in which the paraventricular nucleus might exert such an influence is in instances of stress or fear [7,22], fitting with the presence of the stress hormone corticotropin releasing hormone in this nucleus [97]. It has also been argued that the functional properties of the paraventricular nucleus lie in the realm of visceral processing and visceral feedback regulation [90,123,149]. Functional indications that the paraventricular nucleus is involved in such state-setting and feedback processes is found in its reaction to cocaine administration or exposure to a cocaine-paired environment [19] and its regulation of the level of dopamine utilization in the limbic part of the striatum [70]. Its neighbor the parataenial nucleus has been ascribed, in the words of Kelley and Stinus [75], a role in

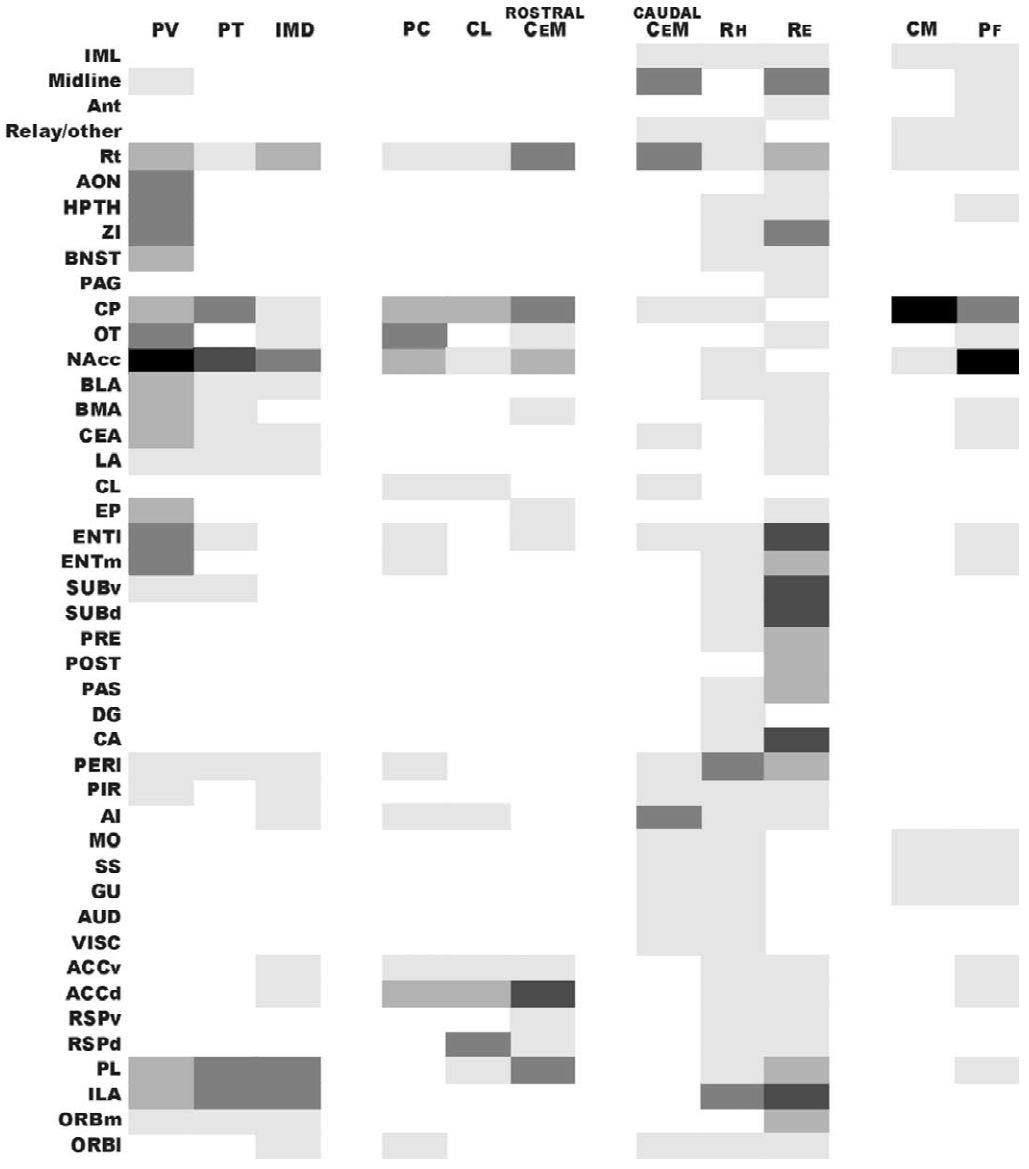

Fig. 13. Diagrammatic representation of the qualitative and quantitative aspects of the patterns of projection from the different midline and intralaminar structures. The nuclei are listed in the top row, the target areas are listed in the column. The degree of blackness indicates the density of projection towards the target areas. Abbreviations: ACCd—dorsal anterior cingulate cortex; ACCv—ventral anterior cingulate cortex; AI—agranular insular cortex; Ant—anterior thalamic nuclei; AON—anterior olfactory nucleus; AUD—auditory cortex; BLA—basolateral amygdala; BMA—basomedial amygdala; BNST—bed nucleus of the stria terminalis; CA—cornu ammonis; CEA—central nucleus of the amygdala; CL—claustrum; CP—caudate putamen; DG—dentate gyrus; ENTm—medial entorhinal cortex; ENTl—lateral entorhinal cortex; EP—endopiriform nucleus; GU—gustatory cortex; HPTH—hypothalamus; ILA—infralimbic cortex; IML—intralaminar nuclei; LA—lateral amygdala; MD—mediodorsal thalamic nucleus; MO—motor cortex; NAcc—nucleus accumbens; ORBl—lateral orbital cortex; ORBm—medial orbital cortex; OT—olfactory tubercle; PAG—periaqueductal grey; PAS—parasubiculum; PERI—perirhinal cortex; PIR—piriform cortex; PL—prelimbic cortex; POST—postsubiculum; PRE—presubiculum; RSPd—dorsal retrosplenial cortex; RSPv—ventral retrosplenial cortex; Rt—reticular thalamic nucleus; SS—somatosensory cortex; SUBd—dorsal subiculum; SUBv—ventral subiculum; VISC—visceral cortex; ZI—zona incerta.

functions such as motivated arousal. Taken together, we propose in analogy to Otake et al. [99] that the functions of the paraventricular nucleus and its neighboring members of the dorsal group can best be classified as ‘viscerolimbic’, more in particular that it plays a role in viscerosensory awareness.

4.3. Lateral group-cognitive awareness

It is well-known that lesioning of the paramedian human thalamus, as seen in cases of trauma, tumors, infarctions and hemorrhages of this area, results in cognitive deficits, including neglect, loss of attention or even hypersomnol-

ence [142]. Interestingly, isolated deficits of memory and higher cognitive functioning have also been described [16]. These effects have consistently been ascribed to the larger cell groups of the thalamus known to be involved in 'limbic circuitry', i.e., the mediodorsal nucleus and the anterior nuclei [117,140,162]. On the basis of the pattern of neural connectivity between the intralaminar and midline nuclei and cortical areas, participation of these nuclei in cognition seems likely, and reports of infarctions affecting intralaminar and midline regions of the thalamus have indeed shown that selective infarctions of portions of the lateral intralaminar structures cause cognitive deficits [45,87,88,152]. These deficits typically take the form of a type of disturbance seen after lesioning of the thalamo-striato-prefrontocortical networks, a so-called dysexecutive syndrome, characterized by a decreased flexibility in the use of cognitive strategies [155].

Similarly, animal experiments lend support for restricted actions of the lateral group of nuclei; lesion studies show that the lateral internal medullary lamina (the PC and CL nuclei) influences working memory rather than reference (long term) memory [78,83,131,172].

Thus, the combined evidence from the clinical reports on lesions of the intralaminar or midline thalamic nuclei with that of the animal experiments, indicate that there is not a global effect of the lateral group on cognition. Rather, some functions are spared, such as anterograde memory formation, whereas especially the executive cognitive functions are at risk. In other words, the role of the lateral group on the memory process does not seem to lie in a contribution to the actual formation of memories, but more in the flexible use of information.

A role in executive processes is in line with the fact that the main cortical output of the lateral group of nuclei is directed towards prefrontal and anterior cingulate cortices, involved in such cognitive processes in the human [14,38,42,43,89,102]. We suggest that the influence of the lateral group of intralaminar and midline nuclei on cognitive capacities is one of 'cognitive awareness', exemplified by the inability of patients or lesioned animals to make flexible use of cognitive strategies, the central aspect of the dysexecutive syndrome.

4.4. Ventral group-polymodal sensory awareness

The distinctive feature of the members of this group is the sparse or absent projection to the striatum, a consistent feature of the other intralaminar and midline nuclei. Instead, they show a widespread projection to the cortex, including the hippocampus proper and parahippocampal cortices, the primary motor and sensory neocortices and associative cortical areas. We propose that the functions of these nuclei lie not so much in the realm of modulation of simple motor or sensory processes, but rather in influencing higher order cognitive, affective and polysensory processing. Functional data on the members of this group are scarce. This is because selective lesions in these nuclei have not been described in humans, and because of the overall size of the nuclei, experimental animal studies are either absent or only scarcely available. In case of the rhomboid nucleus, the small dimensions and the flattened appearance of the nucleus hamper investigation of its functions by experimental means. The posterior part of the central medial nucleus has heretofore not been recognized as a distinct part of this nucleus and a functional role, separate from that of the rostral part, has not been investigated. Some data concerning the role of the reuniens nucleus, however, have been gathered, suggesting a contribution to hippocampal memory processes. The hippocampus can be seen as a final common pathway for the processing of information of the various sensory modalities [163], indicating that the reuniens nucleus might be involved in the modulation of poly- or multimodal information processing. An example of a sensory modality under the influence of modulation by the reuniens nucleus is given by Datiche et al. [29]. These authors argue that the reuniens nucleus might influence olfactory memory at three different steps of processing: through its projections to the piriform cortex, the entorhinal cortex and the hippocampus. Electrophysiological data show that stimulation of the reuniens nucleus results in depolarization of CA1 pyramidal cells, albeit subthreshold for eliciting an action potential. Simultaneously, an activation in presumed inhibitory interneurons of the stratum oriens/alveus occurs [33,36]. Therefore, the reuniens nucleus is able to influence in a double fashion hippocampal information processing.

However, a possible influence of the nucleus reuniens on memory processes remains to be demonstrated, since no human cases of selective lesioning of this nucleus are known. The early degeneration of the nucleus reuniens in Alzheimer's disease [17,18] has been regarded an indication of an involvement in processes of memory, but the evidence is at best circumstantial. Similarly, animal experiments addressing this issue are scarce or nonexistent. Preliminary reports of the effects of selective lesions of the nucleus reuniens in rats support a role in awareness rather than in memory per se [34].

4.5. Posterior group-limbic motor functions: the generation of motor responses following awareness of salient stimuli

The parafascicular and centre médian nuclei differ from the other midline and intralaminar nuclei in the intensity of and preference for the projections towards the basal ganglia. These include the caudate and putamen, and targets unique for the midline and intralaminar nuclei, the globus pallidus, substantia nigra and the subthalamic nucleus. Beckstead [9] noted that the projections from the parafascicular and centre médian completely overlapped

the striatal projections of the other midline and intralaminar nuclei taken together, thereby providing a double innervation of the entire striatum from the thalamus. Parent and Hazrati [104] describe the centre médian as being involved in a closed reciprocal loop with the basal ganglia. The strong connectivity of this group with the motor system of the brain in combination with the relative sparsity of projections to the cortex indicates that its functions may lie in the modulation of motor responses rather than cognitive, emotional, visceral or sensory processes. Data tying its function closely to the control of motor processes are found in the modulation of the level of dopamine turnover in the motor part of the striatum of the rat [76]. Circumstantial evidence is found in the dramatic degeneration of the caudal intralaminar nuclei in motor disorders, i.e., progressive supranuclear palsy and Parkinson's disease [54]. In the words of Cornwall and Phillipson [26], the available anatomical and functional evidence places these nuclei ''very firmly in the context of mechanisms governing motor control''.

Evidence for the involvement of this region in the generation of motor responses comes from studies showing its role in modulation of intracranial self-stimulation behavior and of active avoidance behavior, where a motor response is needed to avoid a footshock [85,49]. A functional differentiation within this group has been suggested. The striatal projection of the centre médian is complementary to that of the Pf. The centre médian projects to the putamen and the lateral or dorsolateral caudate nucleus, whereas the parafascicular nucleus sends fibers preferentially to the medial and ventral parts of the striatum in all species studied. This has led to the proposal that the centre médian is related to sensorimotor aspects of behavior and the parafascicular nucleus is concerned with associative-limbic motor functions [12,104,125–127]. Further indications of a rostral-caudal differentiation within this cluster is found in site-specific effects of lesion and stimulation on motor behavior [151]. Nevertheless, we suggest that the functions of this group as a whole fit with the concept of modulation of motor responses under the influence of external stimuli which the organism perceives as relevant, a concept strongly supported by recent findings of neuronal responses in the centre médian and parafascicular complex of the monkey to behaviorally significant sensory events [86].

5. Concluding remarks

The above delineations of the functions of the four different groups of midline and intralaminar nuclei of the thalamus are necessarily tentative, since data on the functional aspects of these nuclei are lagging behind the knowledge on the anatomical relationships. We have described four clusters of nuclei, each with a different role. We propose that the contribution of the four clusters is similar in type, i.e., supplying arousal to facilitate awareness, but different in the nature of the stimuli that need to be attended to. As a whole, the four clusters would act to maintain a coherent frame of awareness, spanning the realms of emotion, cognition, and sensory as well as motor processes, allowing adaptive behavior in each of these domains. Despite their size, the nuclei are of crucial importance for the integrity of cortical functioning. Paraphrasing Baars [4], who spoke about the involvement of the midline and intralaminar nuclei in the state of waking consciousness, we would like to state that ''surprisingly small subcortical structures are needed for maintaining awareness''.

Acknowledgements

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References

[1] J.P. Aggleton, R. Desimone, M. Mishkin, The origin, course, and termination of the hippocampothalamic projections in the macaque, J. Comp. Neurol. 243 (1986) 409–421.
[2] J.P. Aggleton, M. Mishkin, Projections of the amygdala to the thalamus in the cynomolgus monkey, J. Comp. Neurol. 222 (1984) 56–68.
[3] D.G. Amaral, W.M. Cowan, Subcortical afferents to the hippocampal formation in the monkey, J. Comp. Neurol. 189 (1980) 573–591.
[4] B.J. Baars, Tutorial commentary: surprisingly small subcortical structures are needed for the state of waking consciousness, while cortical projection areas seem to provide perceptual contents of consciousness, Conscious. Cogn. 4 (1995) 159–162.
[5] J.S. Baizer, R. Desimone, L.G. Ungerleider, Comparison of subcortical connections of inferior temporal and posterior parietal cortex in monkeys, Vis. Neurosci. 10 (1993) 59–72.
[6] G. Balercia, K. Kultas-Ilinsky, M. Bentivoglio, I.A. Ilinsky, Neuronal and synaptic organization of the centromedian nucleus of the monkey thalamus: a quantitative ultrastructural study, with tract tracing and immunohistochemical observations, J. Neurocytol. 25 (1996) 267–288.
[7] C.H.M. Beck, H.C. Fibiger, Conditioned fear-induced changes in behavior and in the expression of the immediate early gene c-fos: with and without diazepam treatment, J. Neurosci. 15 (1995) 709–720.
[8] R.M. Beckstead, Afferent connections of the entorhinal area in the rat as demonstrated by retrograde cell-labelling with horseradish peroxidase, Brain Res. 152 (1978) 249–264.
[9] R.M. Beckstead, The thalamostriatal projection in the cat, J. Comp. Neurol. 223 (1984) 313–346.
[10] M. Bentivoglio, G. Macchi, A. Albanese, The cortical projections of the thalamic intralaminar nuclei, as studied in cat and rat with the multiple fluorescent retrograde tracing technique, Neurosci. Lett. 26 (1981) 5–10.
[11] M. Bentivoglio, G. Balercia, L. Kruger, The specificity of the non-specific thalamus: the midline nuclei, in: G. Holstege (Ed.), Progress in Brain Research, Vol. 87, Elsevier, Amsterdam, 1991, pp. 53–80.
[12] H.W. Berendse, H.J. Groenewegen, Organization of the thalamos-

triatal projections in the rat, with special emphasis on the ventral striatum, J. Comp. Neurol. 299 (1990) 187–228.
[13] H.W. Berendse, H.J. Groenewegen, Restricted cortical termination fields of the midline and intralaminar thalamic nuclei in the rat, Neuroscience 42 (1991) 73–102.
[14] K.F. Berman, J.L. Ostrem, C. Randolph, J. Gold, T.E. Goldberg, R. Coppola, R.E. Carson, P. Herscovitch, D.R. Weinberger, Physiological activation of a cortical network during performance of the wisconsin card sorting test: a positron emission tomography study, Neuropsychologia 33 (1995) 1027–1046.
[15] P. Bobillier, S. Seguin, A. Degueurce, B.D. Lewis, J.F. Pujol, The efferent connections of the nucleus raphe centralis superior in the rat as revealed by autoradiography, Brain Res. 166 (1979) 1–8.
[16] J. Bogousslavsky, F. Regli, A. Uske, Thalamic infarcts: clinical syndromes, etiology and prognosis, Neurology 38 (1988) 837–848.
[17] H. Braak, E. Braak, Alzheimer's disease affects limbic nuclei of the thalamus, Acta Neuropathol. 81 (1991) 261–268.
[18] H. Braak, E. Braak, Evolution of neuronal changes in the course of Alzheimer's disease, J. Neural Transm. Suppl. 53 (1998) 127–140.
[19] E.E. Brown, G.S. Robertson, H. C Fibiger, Evidence for conditional neuronal activation following exposure to a cocaine-paired environment: role of forebrain limbic structures, J. Neurosci. 12 (1992) 4112–4121.
[20] J. Carlsen, L. Heimer, The projection from the parataenial thalamic nucleus, as demonstrated by the phaseolus vulgaris-leucoagglutinin (PHA-L) method, identifies a subterritorial organization of the ventral striatum, Brain Res. 374 (1986) 375–379.
[21] P. Cesaro, J. Nguyen-Legros, B. Pollin, S. Laplante, Single intralaminar thalamic neurons project to cerebral cortex, striatum and nucleus reticularis thalami. A retrograde anatomical tracing study in the rat, Brain Res. 325 (1985) 29–37.
[22] N. Chastrette, D.W. Pfaff, R.B. Gibbs, Effects of daytime and nighttime stress on Fos-like immunoreactivity in the paraventricular nucleus of the hypothalamus, the habenula, and the posterior paraventricular nucleus of the thalamus, Brain Res. 563 (1991) 339–344.
[23] S. Chen, H.-S. Su, Afferent connections of the thalamic paraventricular and parataenial nuclei in the rat—a retrograde tracing study with iontophoretic application of fluoro-gold, Brain Res. 522 (1990) 1–6.
[24] J. Chen, S. Zeng, Z. Rao, J. Shi, Serotonergic projections from the midbrain periaqueductal gray and nucleus raphe dorsalis to the nucleus parafascicularis of the thalamus, Brain Res. 584 (1992) 294–298.
[25] P.E. Comans, P.J. Snow, Ascending projections to nucleus parafascicularis of the cat, Brain Res. 230 (1981) 337–341.
[26] J. Cornwall J, O.T. Phillipson, Afferent projections to the parafascicular thalamic nucleus of the rat, as shown by the retrograde transport of wheat germ agglutinin, Brain Res. Bull. 20 (1988) 139–150.
[27] J. Cornwall, O.T. Phillipson, Afferent projections to the dorsal thalamus of the rat as shown by retrograde lectin transport. II. The midline nuclei, Brain Res. Bull. 21 (1988) 147–161.
[28] J. Cornwall, J.D. Cooper, O.T. Phillipson, Projections to the rostral reticular thalamic nucleus in the rat, Exp. Brain Res. 80 (1990) 157–171.
[29] F. Datiche, P.H. Luppi, M. Cattarelli, Projection from nucleus reuniens thalami to piriform cortex: a tracing study in the rat, Brain Res. Bull. 38 (1995) 87–92.
[30] S. De Las Heras, E. Mengual, J.M. Gimenez-Amaya, Double retrograde tracer study of the thalamostriatal projections to the cat caudate nucleus, Synapse 32 (1999) 80–92.
[31] M. Deschenes, J. Bourassa, V. Diep Doan, A. Parent, A single cell study of the axonal projections arising from the posterior intralaminar thalamic nuclei in the rat, Eur. J. Neurosci. 8 (1996) 329–343.
[32] M.J. Dolleman-Van Der Weel, W. Ang, M.P. Witter, Afferent connections of the nucleus reuniens thalami: a neuroanatomical tracing study in the rat, Eur. J. Neurosci. Suppl. 6 (1993) 65.
[33] M.J. Dolleman-Van Der Weel, F.H. Lopes da Silva, M.P. Witter, Nucleus reuniens thalami modulates activity in hippocampal field CA1 through excitatory and inhibitory mechanisms, J. Neurosci. 17 (1997) 5640–5650.
[34] M.J. Dolleman-Van Der Weel, R.G.M. Morris, M.P. Witter, Ibotenate lesions of the nucleus reuniens thalami fail to impair spatial learning and memory, Soc. Neurosci. Abstr. 20 (1994) 1212.
[35] M.J. Dolleman-Van Der Weel, M.P. Witter, Projections from the nucleus reuniens thalami to the entorhinal cortex, hippocampal field CA1, and the subiculum in the rat arise from different populations of neurons, J. Comp. Neurol. 364 (1995) 637–650.
[36] M.J. Dolleman-Van Der Weel, M.P. Witter, Nucleus reuniens thalami innervates GABAergic interneurons in hippocampal field CA1 of the rat, Neurosci. Lett. 278 (2000) 145–148.
[37] W.K. Dong, H. Ryu, I.H. Wagman, Nociceptive responses of neuron in medial thalamus and their relationship to spinothalamic pathways, J. Neurophysiol. 41 (1978) 1592–1613.
[38] J.D. Duffy, J.J. Campbell, The regional prefrontal syndromes: a theoretical and clinical overview, J. Neuropsychiatry Clin. Neurosci. 6 (1994) 379–387.
[39] J. Feger, M. Bevan, A.R. Crossman, The projections from the parafascicular thalamic nucleus to the subthalamic nucleus and the striatum arise from separate neuronal populations: a comparison with the corticostriatal and corticosubthalamic efferents in a retrograde fluorescent double-labelling study, Neuroscience 60 (1994) 125–132.
[40] D.M. Finch, E.L. Derian, T.L. Babb, Afferent fibers to rat cingulate cortex, Exp. Neurol. 83 (1984) 468–485.
[41] P. Fiset, T. Paus, T. Daloze, G. Plourde, P. Meuret, V. Bonhomme, N. Hajj-Ali, S.B. Backmann, A.C. Evans, Brain mechanisms of propofol-induced loss of consciousness in humans: a positron emission tomographic study, J. Neurosci. 19 (1999) 5506–5513.
[42] J.M. Fuster, Frontal lobe syndromes, in: B.S. Fogel, R.B. Schiffer, S.M. Rao (Eds.), Neuropsychiatry, William and Wilkins, Baltimore, MD, 1996, pp. 407–415.
[43] J.M. Fuster, in: The Prefrontal Cortex. Anatomy, Physiology and Neuropsychology of the Frontal Lobe, 2nd Edition, Raven Press, New York, 1988, pp. 136–138.
[44] G.J. Giesler Jr., H.R. Spiel, W.D. Willis, Organization of spinothalamic tract axons within the rat spinal cord, J. Comp. Neurol. 195 (1981) 243–252.
[45] N.R. Graff-Radford, D. Tranel, G.W. Van Hoesen, J.P. Brandt, Diencephalic amnesia, Brain 113 (1990) 1–25.
[46] H.J. Groenewegen, Organization of the afferent connections of the mediodorsal thalamic nucleus in the rat, related to the mediodorsal-prefrontal topography, Neuroscience 24 (1988) 379–431.
[47] H.J. Groenewegen, H.W. Berendse, The specificity of the 'non-specific' midline and intralaminar thalamic nuclei, Trends Neurosci. 17 (1994) 52–57.
[48] R.W. Guillery, Anatomical evidence concerning the role of the thalamus in corticocortical communication: a brief review, J. Anat. 187 (1995) 583–592.
[49] G. Guillazo-Blanch, A.M. Vale-Martinez, M. Marti-Nicolovius, M. Coll-Andreu, I. Morgado-Bernal, The parafascicular nucleus and two-way active avoidance: effects of electrical stimulation and electrode implantation, Exp. Brain Res. 129 (1999) 605–614.
[50] W.O. Guldin, H.J. Markowitsch, Cortical and thalamic afferent connections of the insular and adjacent cortex of the rat, J. Comp. Neurol. 215 (1983) 135–153.
[51] A.E. Hallanger, A.I. Levey, H.J. Lee, D.B. Rye, B.H. Wainer, The origins of cholinergic and other subcortical afferents to the thalamus in the rat, J. Comp. Neurol. 262 (1987) 105–124.
[52] A.J. Haroian, L.C. Massopust, P.A. Young, Cerebellothalamic projections in the rat: an autoradiographic and degeneration study, J. Comp. Neurol. 197 (1981) 217–236.
[53] R.W. Hautvast, G.J. Ter Horst, B.M. De Jong, M.J. De Jongste, P.K. Blanksma, A.M. Paans, J. Korf, Relative changes in regional

cerebral blood flow during spinal cord stimulation in patients with refractory angina pectoris, Eur. J. Neurosci. 9 (1997) 1178–1183.
[54] J.M. Henderson, K. Carpenter, H. Cartwright, G.M. Halliday, Loss of thalamic intralaminar nuclei in progressive supranuclear palsy and Parkinson's disease: clinical and therapeutic implications, Brain 123 (2000) 1410–1421.
[55] M. Herkenham, The connections of the nucleus reuniens thalami: evidence for a direct thalamo-hippocampal pathway in the rat, J. Comp. Neurol. 177 (1978) 589–610.
[56] M. Herkenham, Laminar organization of thalamic projections to the rat neocortex, Science 207 (1980) 532–535.
[57] R.W. Hunsperger, D. Roman, The integrative role of the intralaminar system of the thalamus in visual orientation and perception in the cat, Exp. Brain Res. 25 (1976) 231–246.
[58] J. Hunter, H.H. Jasper, Effects of thalamic stimulation in unanaesthetised animals. The arrest reaction and petit mal-like seizures, activation patterns and generalized convulsions, Electroencephalogr. Clin. Neurophysiol. 1 (1949) 305–324.
[59] K.M. Hurley, H. Herbert, M.M. Moga, C.B. Saper, Efferent projections of the infralimbic cortex of the rat, J. Comp. Neurol. 308 (1991) 249–276.
[60] R. Insausti, D.G. Amaral, W.M. Cowan, The entorhinal cortex of the monkey: III. Subcortical afferents, J. Comp. Neurol. 264 (1987) 396–408.
[61] H.H. Jasper, Diffuse projection systems: the integrative action of the thalamic reticular system, Electroencephalogr. Clin. Neurophysiol. 1 (1949) 405–420.
[62] H.H. Jasper, Unspecific thalamocortical relations, in: J. Field, H.W. Magoun, V.E. Hall (Eds.), Handbook of Physiology, Vol. 2, American Physiological Society, Washington, DC, 1960, pp. 1307–1321, Section 1.
[63] H.H. Jasper, Sensory information and conscious experience, in: H.H. Jasper, L. Descarries, V.F. Castellucci, S. Rossignol (Eds.), Consciousness: At the Frontiers of Neuroscience, Advances in Neurology, Vol. 77, Lippincott-Raven, Philadelphia, PA, 1998, pp. 33–48.
[64] A. Jayaraman, Organization of thalamic projections in the nucleus accumbens and the caudate nucleus in cats and its relation with hippocampal and other subcortical afferents, J. Comp. Neurol. 231 (1985) 396–420.
[65] P. Johannsen, J. Jakobsen, P. Bruhn, S.B. Hansen, A. Gee, H. Stodkilde-Jorgensen, A. Gjedde, Cortical sites of sustained and divided attention in normal elderly humans, Neuroimage 6 (1997) 145–155.
[66] B.F. Jones, M.P. Witter, Cingulate cortex projections to the (para)hippocampal area in the rat: an anatomical tracer study, Soc. Neurosci. Abstr. 25 (part I) (1999) 891.
[67] E.G. Jones, R.Y. Leavitt, Retrograde axonal transport and the demonstration of non-specific projections to the cerebral cortex and striatum from thalamic intralaminar nuclei in the rat, cat and monkey, J. Comp. Neurol. 154 (1974) 349–378.
[68] E.G. Jones, The Thalamus, Plenum Press, New York, 1985.
[69] E.G. Jones, A new view of specific and nonspecific thalamocortical connections, in: H.H. Jasper, L. Descarries, V.F. Castellucci, S. Rossignol (Eds.), Consciousness: At the Frontiers of Neuroscience, Advances in Neurology, Vol. 77, Lippincott-Raven, Philadelphia, PA, 1998, pp. 49–71.
[70] M.W. Jones, I.C. Kilpatrick, O.T. Phillipson, Regulation of dopamine function in the nucleus accumbens of the rat by the thalamic paraventricular nucleus and adjacent midline nuclei, Exp. Brain Res. 76 (1989) 572–580.
[71] S.S. Kaitz, R.T. Robertson, Thalamic connections with limbic cortex. II. Corticothalamic projections, J. Comp. Neurol. 195 (1981) 527–545.
[72] N. Kajimura, M. Uchiyama, Y. Takayama, S. Uchida, T. Uema, M. Kato, M. Sekimoto, T. Watanabe, T. Nakajima, S. Horikoshi, K. Ogawa, M. Nishikawa, M. Hiroki, Y. Kudo, H. Matsuda, M. Okawa, K. Takahashi, Activity of midbrain reticular formation and neocortex during the progression of human non-rapid eye movement sleep, J. Neurosci. 19 (1999) 10065–10073.
[73] E.F.S. Kaufman, A.C. Rosenquist, Efferent connections of the thalamic intralaminar nuclei in the cat, Brain Res. 335 (1985) 257–279.
[74] E.F.S. Kaufman, A.C. Rosenquist, Afferent connections of the thalamic intralaminar nuclei in the cat, Brain Res. 335 (1985) 281–296.
[75] A.E. Kelley, L. Stinus, The distribution of the projection from the parataenial nucleus of the thalamus to the nucleus accumbens in the rat: an autoradiographic study, Exp. Brain Res. 54 (1984) 499–512.
[76] I.C. Kilpatrick, M.W. Jones, B.J. Johnson, J. Cornwall, O.T. Phillipson, Thalamic control of dopaminergic functions in the caudate-putamen of the rat II. Studies using ibotenic acid injection of the parafascicular-intralaminar nuclei, Neuroscience 19 (1986) 979–990.
[77] S. Kinomura, J. Larsson, B. Gulyas, P.E. Roland, Activation of the human reticular formation and thalamic intralaminar nuclei, Science 271 (1996) 512–515.
[78] S.M. Koger, R.G. Mair, Comparison of the effects of frontal cortical and thalamic lesions on measures of olfactory learning and memory in the rat, Behav. Neurosci. 108 (1994) 1088–1100.
[79] J.E. Krettek, J.L. Price, The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat, J. Comp. Neurol. 171 (1977) 157–192.
[80] W.J.S. Krieg, The medial region of the thalamus of the albino rat, J. Comp. Neurol. 80 (1944) 381–415.
[81] R.R. Llinas, D. Paré, Of dreaming and wakefulness, Neuroscience 44 (1991) 521–535.
[82] G. Macchi, M. Bentivoglio, C. D'Atena, P. Rossini, E. Tempesta, The cortical projections of the thalamic intralaminar nuclei restudied by means of the HRP retrograde axonal transport, Neurosci. Lett. 4 (1977) 121–126.
[83] R.G. Mair, D.M. Lacourse, Radiofrequency lesions of the thalamus produce delayed-nonmatching-to-sample impairments comparable to pyrithiamine-induced encephalopathy in rats, Behav. Neurosci. 106 (1992) 634–645.
[84] P. Maquet, J. Peters, J. Aerts, G. Delfiore, C. Degueldre, A. Luxen, G. Franck, Functional neuroanatomy of human rapid-eye-movement sleep and dreaming, Nature 383 (1996) 163–166.
[85] E. Massanes-Rotger, L. Aldavert-Vera, P. Segura-Torres, M. Marti-Nicolovius, I. Morgado-Bernal, Involvement of the parafascicular nucleus in the facilitative effect of intracranial self-stimulation on active avoidance in rats, Brain Res. 808 (1998) 220–231.
[86] N. Matsumoto, T. Minanimoto, A.M. Graybiel, M. Kimura, Neurons in the thalamic CM-Pf complex supply striatal neurons with information about behaviorally significant sensory events, J. Neurophysiol. 85 (2001) 960–976.
[87] M. Mennemeier, E. Fennell, E. Valenstein, K.M. Heilman, Contributions of the left intralaminar and medial thalamic nuclei to memory. Comparisons and report of a case, Arch. Neurol. 49 (1992) 1050–1058.
[88] M. Mennemeier, B. Crosson, D.J. Willliamson, S.E. Nadeau, E. Fennell, E. Valenstein, K.M. Heilman, Tapping talking and the thalamus: possible influence of the intralaminar nuclei on basal ganglia function, Neuropsychologia 35 (1997) 183–193.
[89] B. Milner, M. Petrides, Behavioural effects of frontal-lobe lesions in man, Trends Neurosci. 7 (1984) 403–407.
[90] M.M. Moga, R.P. Weis, R.Y. Moore, Efferent projections of the paraventricular thalamic nucleus in the rat, J. Comp. Neurol. 359 (1995) 221–238.
[91] G. Moruzzi, H.W. Magoun, Brain stem reticular formation and activation of the EEG, Electroencephalogr. Clin. Neurophysiol. 1 (1949) 455–473.
[92] M.C. Münkle, H.J. Waldvogel, R.L.M. Faull, The distribution of calbindin, calretinin and parvalbumin immunoreactivity in the human thalamus, J. Chem. Neuroanat. 19 (2000) 155–173.

[93] S.Y. Musil, C.R. Olson, Organization of cortical and subcortical projections to anterior cingulate cortex in the cat, J. Comp. Neurol. 272 (1988) 203–218.
[94] D.B. Newman, C.Y. Ginsberg, Brainstem reticular nuclei that project to the thalamus in rats: a retrograde tracer study, Brain. Behav. Evol. 44 (1994) 1–39.
[95] K. Niimi, H. Matsuoka, T. Aisaka, Y. Okada, Thalamic afferents to the prefrontal cortex in the cat traced with horseradish peroxidase, J. Hirnforsch. 22 (1981) 221–241.
[96] T. Ohtake, H. Yamada, Efferent connections of the nucleus reuniens and the rhomboid nucleus in the rat: an anterograde PHA-L tracing study, Neurosci. Res. 6 (1989) 556–568.
[97] K. Otake, Y. Nakamura, Sites of origin of corticotropin-releasing factor-like immunoreactive projection fibers to the paraventricular thalamic nucleus in the rat, Neurosci. Lett. 201 (1995) 84–86.
[98] K. Otake, D.A. Ruggiero, Monoamines and nitric oxide are employed by afferents engaged in midline thalamic regulation, J. Neurosci. 15 (1995) 1891–1911.
[99] K. Otake, D.A. Ruggiero, Y. Nakamura, Adrenergic innervation of forebrain neurons that project to the paraventricular thalamic nucleus in the rat, Brain Res. 697 (1995) 17–26.
[100] O.P. Ottersen, Y. Ben-Ari, Demonstration of a heavy projection of midline thalamic neurons upon the lateral nucleus of the amygdala of the rat, Neurosci. Lett. 9 (1978) 147–152.
[101] O.P. Ottersen, Y. Ben-Ari, Afferent connections to the amygdaloid complex of the rat and cat. I. Projections from the thalamus, J. Comp. Neurol. 187 (1979) 401–424.
[102] A.M. Owen, The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging, Eur. J. Neurosci. 9 (1997) 1329–1339.
[103] P. Panula, U. Pirvola, S. Auvinen, M.S. Airaksinen, Histamine-immunoreactive nerve fibers in the rat brain, Neuroscience 28 (1989) 585–610.
[104] A. Parent, L.N. Hazrati, Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop, Brain Res. Rev. 20 (1995) 91–127.
[105] T. Paus, R.J. Zatorre, N. Hofle, Z. Caramanos, J. Gotman, M. Petrides, A.C. Evans, Time-related changes in neural systems underlying attention and arousal during the performance of an auditory vigilance task, J. Cogn. Neurosci. 9 (1997) 392–408.
[106] G. Paxinos, C. Watson, The Rat Brain in Stereotaxic Coordinates, 2nd Edition, Academic Press, Sydney, 1986.
[107] M. Peschanski, J.M. Besson, A spino-reticulo-thalamic pathway in the rat: an anatomical study with reference to pain transmission, Neuroscience 12 (1984) 165–178.
[108] P. Petrovicky, Thalamic descendents from anterior and parafascicular nuclei to the brainstem. An experimental study using the HRP technique in the rat, J. Hirnforsch. 24 (1983) 329–339.
[109] C.M. Portas, K. Krakow, P. Allen, O. Josephs, J.L. Armony, C.D. Frith, Auditory processing across the sleep–wake cycle: simultaneous EEG and fMRI monitoring in humans, Neuron 28 (2000) 991–999.
[110] K.P. Purpura, N.D. Schiff, The thalamic intralaminar nuclei: a role in visual awareness, Neuroscientist 3 (1997) 8–15.
[111] P. Rainville, G.H. Duncan, D.D. Price, B. Carrier, M.C. Bushnell, Pain affect encoded in human anterior cingulate but not somatosensory cortex, Science 277 (1997) 968–971.
[112] R.L. Reep, S.S. Winans, Afferent connections of dorsal and ventral agranular insular cortex in the hamster *Mesocricetus auratus*, Neuroscience 7 (1982) 1265–1288.
[113] B. Rico, C. Cavada, Adrenergic innervation of the monkey thalamus: an immunohistochemical study, Neuroscience 84 (1998) 839–847.
[114] J.N. Riley, R.Y. Moore, Diencephalic and brainstem afferents to the hippocampal formation, Brain Res. Bull. 6 (1981) 437–444.
[115] P.Y. Risold, R.H. Tompson, L.W. Swanson, The structural organisation of connections between hypothalamus and cerebral cortex, Brain Res. Rev. 24 (1997) 197–254.
[116] R.T. Robertson, S.S. Kaitz, Thalamic connections with limbic cortex. I. Thalamocortical projections, J. Comp. Neurol. 195 (1981) 501–525.
[117] M. Roisseau, Amnesias following limited thalamic infarctions, in: J. Delacour (Ed.), The Memory System of the Brain, Adv. Series Neurosci., Vol. 4, World Scientific Publishers, Singapore, New Jersey, London, 1994, pp. 241–277.
[118] G.J. Royce, Cells of origin of corticothalamic projections upon the centromedian and parafascicular nuclei in the cat, Brain Res. 258 (1983) 11–21.
[119] G.J. Royce, Cortical neurons with collateral projections to both the caudate nucleus and the centromedian-parafascicular thalamic complex: a fluorescent retrograde double labeling study in the cat, Exp. Brain Res. 50 (1983) 157–165.
[120] G.J. Royce, Single thalamic neurons which project to both the rostral cortex and caudate nucleus studied with the fluorescent double labeling method, Exp. Neurol. 79 (1983) 773–784.
[121] G.J. Royce, R.J. Mourey, Efferent connections of the centromedian and parafascicular thalamic nuclei: an autoradiographic investigation in the cat, J. Comp. Neurol. 235 (1985) 277–300.
[122] G.J. Royce, S. Bromley, C. Gracco, Subcortical projections to the centromedian and parafascicular thalamic nuclei in the rat, J. Comp. Neurol. 306 (1991) 129–155.
[123] D.A. Ruggiero, S. Anwar, J. Kim, S.B. Glickstein, Visceral afferent pathways to the thalamus and olfactory tubercle: behavioral implications, Brain Res. 799 (1998) 159–171.
[124] F.T. Russchen, Amygdalopetal projections in the cat. II. Subcortical afferent connections. A study with retrograde tracing techniques, J. Comp. Neurol. 207 (1982) 157–176.
[125] A.F. Sadikot, A. Parent, C. Francois, The centre médian and parafascicular thalamic nuclei project, respectively to the sensorimotor and associative-limbic striatal territories in the squirrel monkey, Brain Res. 510 (1990) 161–165.
[126] A.F. Sadikot, A. Parent, C. Francois, Efferents connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a PHA-L study of subcortical projections, J. Comp. Neurol. 315 (1992) 137–159.
[127] A.F. Sadikot, A. Parent, Y. Smith, J.P. Bolam, Efferent connections of the centromedian and parafascicular thalamic nuclei in the squirrel monkey: a light and electron microscopic study of the thalamostriatal projection in relation to striatal heterogeneity, J. Comp. Neurol. 320 (1992) 228–242.
[128] S.T. Sakai, K. Patton, Distribution of cerebellothalamic and nigrothalamic projections in the dog: a double anterograde tracing study, J. Comp. Neurol. 330 (1993) 183–194.
[129] S.T. Sakai, A. Smith, Distribution of nigrothalamic projections in the dog, J. Comp. Neurol. 318 (1992) 83–92.
[130] S.T. Sakai, D. Tanaka Jr., Contralateral corticothalamic projections from area 6 in the raccoon, Brain Res. 299 (1984) 371–375.
[131] L.M. Savage, A.J. Sweet, R. Castillo, P.J. Langlais, The effects of lesions to thalamic lateral internal medullary lamina and posterior nuclei on learning, memory and habituation in the rat, Behav. Brain Res. 82 (1997) 133–147.
[132] J.D. Schall, Visuomotor areas of the frontal lobe, in: K.S. Rockland, A. Peters, J.H. Kaas (Eds.), Cerebral Cortex: Extrastriate Cortex of Primates, Vol. 14, Plenum Press, New York, 1997, pp. 527–638.
[133] N.D. Schiff, S. Frucht, K.P. Purpura, D.A. Ruggiero, The crises of Von Economo: a dystonia of the intralaminar-midline thalamic complex?, Soc. Neurosci. Abstr. 25 (1999) 375.
[134] J. Schlag, M. Schlag-Rey, Visuomotor functions of central thalamus in monkey. II. Unit activity related to visual events, targeting, and fixation, J. Neurophysiol. 51 (1984) 1175–1195.
[135] M. Schlag-Rey, J. Schlag, Visuomotor functions of central thalamus in monkey. I. Unit activity related to spontaneous eye movements, J. Neurophysiol. 51 (1984) 1149–1174.
[136] S.R. Sesack, A.Y. Deutch, R.H. Roth, B.S. Bunney, Topographical

organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with *Phaseolus vulgaris* leucoagglutinin, J. Comp. Neurol. 290 (1989) 213–242.
[137] T. Shiroyama, T. Kayahara, Y. Yasui, J. Nomura, K. Nakano, The vestibular nuclei of the rat project to the lateral part of the thalamic parafascicular nucleus (centromedian nucleus in primates), Brain Res. 704 (1995) 130–134.
[138] G.L. Shulman, M. Corbetta, R.L. Buckner, J.A. Fiez, F.M. Miezin, M.E. Raichle, S.E. Petersen, Common blood flow changes across visual tasks: I. Increases in subcortical structures and cerebellum but not in nonvisual cortex, J. Cogn. Neurosci. 9 (1997) 624–647.
[139] J. Smythies, The functional neuroanatomy of awareness: with a focus on the role of various anatomical systems in the control of intermodal attention, Conscious. Cogn. 6 (1997) 455–481.
[140] L.R. Squire, R.Y. Moore, Dorsal thalamic lesions in a noted case of human memory dysfunction, Ann. Neurol. 6 (1979) 603–606.
[141] M. Steriade, E.G. Jones, D.A. McCormick, Thalamic organization and chemical anatomy, in: Thalamus, Organisation and Function, Vol. I, Elsevier, Amsterdam, 1997, pp. 31–174.
[142] M. Steriade, Thalamic substrates of disturbances in states of vigilance and consciousness in humans, in: M. Steriade, E.G. Jones, D.A. McCormick (Eds.), Thalamus, Experimental and Clinical Aspects, Vol. II, Elsevier, Amsterdam, 1997, pp. 721–742.
[143] M. Steriade, L.L. Glenn, Neocortical and caudate projections of intralaminar thalamic neurons and their synaptic excitation from midbrain reticular core, J. Neurophysiol. 48 (1982) 352–371.
[144] W. Sturm, A. De Simone, B.J. Krause, K. Specht, V. Hesselmann, I. Radermacher, H. Herzog, L. Tellmann, H.W. Müller-Gärtner, K. Willmes, Functional anatomy of intrinsic alertness: evidence for a fronto-parietal-thalamic-brainstem network in the right hemisphere, Neuropsychologia 37 (1999) 797–805.
[145] H.S. Su, M. Bentivoglio, Thalamic midline cell populations projecting to the nucleus accumbens, amygdala, and hippocampus in the rat, J. Comp. Neurol. 297 (1990) 582–593.
[146] L.W. Swanson, Brainmaps: Structure of the Rat Brain, Elsevier, Amsterdam, 1992.
[147] M. Takada, K.J. Campbell, T. Moriizumi, T. Hattori, On the origin of the dopaminergic innervation of the paraventricular thalamic nucleus, Neurosci. Lett. 115 (1990) 33–36.
[148] S.M. Thompson, R.T. Robertson, Organization of subcortical pathways for sensory projections to the limbic cortex I. Subcortical projections to the medial limbic cortex in the rat, J. Comp. Neurol. 265 (1987) 175–188.
[149] B.H. Turner, M. Herkenham, Thalamoamygdaloid projections in the rat: a test of the amygdala's role in sensory processing, J. Comp. Neurol. 313 (1991) 295–325.
[150] J. Ullan, Cortical topography of thalamic intralaminar nuclei, Brain Res. 328 (1985) 333–340.
[151] A. Vale-Martinez, M. Marti-Nicolovius, G. Guillazo-Blanch, I. Morgado-Bernal, Differential site-specific effects of parafascicular stimulation on active avoidance in rats, Behav. Brain Res. 93 (1998) 107–118.
[152] Y.D. Van Der Werf, J.G.E. Weerts, J. Jolles, M.P. Witter, J. Lindeboom, P. Scheltens, Neuropsychological correlates of a right unilateral lacunar thalamic infarction, J. Neurol. Neurosurg. Psychiatry 66 (1999) 36–42.
[153] Y.D. Van Der Werf, M.P. Witter, Are the midline nuclei of the thalamus involved in cognitive functioning? A neuroanatomical account, Soc. Neurosci. Abstr. 25 (part II) (1999) 1889.
[154] Y.D. Van Der Werf, M.P. Witter, P. Scheltens, J. Jolles J, Lateralization of neuropsychological effects after lesions of the thalamus, Eur. J. Neurosci. 10 (suppl. 10) (1998) 143.
[155] Y.D. Van Der Werf, M.P. Witter, H.B.M. Uylings, J. Jolles, Neuropsychology of infarctions in the thalamus; a meta-analysis, Neuropsychologia 38 (2000) 613–627.
[156] R.P. Vertes, A PHA-L analysis of ascending projections of the dorsal raphe nucleus in the rat, J. Comp. Neurol. 313 (1991) 643–668.
[157] R.P. Vertes, PHA-L analysis of projections from the supramammillary nucleus in the rat, J. Comp. Neurol. 326 (1992) 595–622.
[158] R.P. Vertes, G.F. Martin, Autoradiographic analysis of ascending projections from the pontine and mesencephalic reticular formation and the median raphe nucleus in the rat, J. Comp. Neurol. 275 (1988) 511–541.
[159] L. Villanueva, C. Desbois, D. Le Bars, J.F. Bernard, Organization of diencephalic projections from the medullary subnucleus reticularis and the adjacent cuneate nucleus: a retrograde and anterograde tracer study in the rat, J. Comp. Neurol. 390 (1998) 133–160.
[160] B.A. Vogt, D.N. Pandya, D.L. Rosene, Cingulate cortex of the rhesus monkey: I. Cytoarchitecture and thalamic afferents, J. Comp. Neurol. 262 (1987) 256–270.
[161] B.A. Vogt, D.L. Rosene, D.N. Pandya, Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey, Science 204 (1979) 205–207.
[162] D.Y. Von Cramon, N. Hebel, U. Schuri, A contribution to the anatomical basis of thalamic amnesia, Brain 108 (1985) 993–1008.
[163] M.P. Witter, H.J. Groenewegen, F.H. Lopes Da Silva, A.H.M. Lohman, Functional organization of the extrinsic and intrinsic circuitry of the parahippocampal region, Prog. Neurobiol. 33 (1989) 161–253.
[164] M.P. Witter, R.H. Ostendorf, H.J. Groenewegen, Heterogeneity in the dorsal subiculum of the rat. Distinct neuronal zones project to different cortical and subcortical targets, Eur. J. Neurosci. 2 (1990) 718–725.
[165] F.G. Wouterlood, E. Saldana, M.P. Witter, Projection from the nucleus reuniens thalami to the hippocampal region: light and electron microscopic tracing study in the rat with the anterograde tracer phaseolus vulgaris-leucoagglutinin, J. Comp. Neurol. 296 (1990) 179–203.
[166] C.I. Wright, H.J. Groenewegen, Patterns of convergence and segregation in the medial nucleus accumbens of the rat: relationships of prefrontal cortical, midline thalamic, and basal amygdaloid afferents, J. Comp. Neurol. 361 (1995) 383–403.
[167] C.I. Wright, H.J. Groenewegen, Patterns of overlap and segregation between insular cortical intermediodorsal thalamic and basal amygdaloid afferents in the nucleus accumbens of the rat, Neuroscience 73 (1996) 359–373.
[168] J.M. Wyss, L.W. Swanson, W.M. Cowan, A study of subcortical afferents to the hippocampal formation in the rat, Neuroscience 4 (1979) 463–476.
[169] D.S.G. Yamasaki, G.M. Krauthamer, R.W. Rhoades, Superior collicular projection to intralaminar thalamus in rat, Brain Res. 378 (1986) 223–233.
[170] M. Yanagihara, K. Niimi, K. Ono, Thalamic projections to the hippocampal and entorhinal areas in the cat, J. Comp. Neurol. 266 (1987) 122–141.
[171] E.H. Yeterian, D.N. Pandya, Thalamic connections of the cortex of the superior temporal sulcus in the rhesus monkey, J. Comp. Neurol. 282 (1989) 80–97.
[172] H.L. Young, A.A. Stevens, E. Converse, R.G. Mair, A comparison of temporal decay in place memory tasks in rats (*Rattus norvegicus*) with lesions affecting thalamus, frontal cortex, or the hippocampal system, Behav. Neurosci. 110 (1996) 1244–1260.