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New Perspectives on the Organization and Evolution of Nonspecific Thalamocortical Projections

MILES HERKENHAM

1. Historical Origins of the Term “Nonspecific Thalamus”

Lorente de Nó (1938) provided the classic description of two contrasting thalamic afferent fiber types in the rodent neocortex. His Golgi material showed “specific” fibers, which arborize densely in very restricted cortical domains, and “nonspecific” fibers, which distribute sparsely across large cortical expanses. These initial anatomical observations were embraced by electrophysiologists who electrically stimulated thalamic nuclei in cats and recorded two fundamentally different kinds of cortical response, depending on the locus of stimulation. “Specific” and “nonspecific” thalamic nuclei were named according to their ability to elicit restricted cortical “augmenting” or widespread “recruiting” responses, respectively (Morison and Dempsey, 1942; Dempsey and Morison, 1942b). During the 1940s and 1950s a consensus took hold—that the specific system defined ana-

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tomically was the same as that defined electrophysiologically and, likewise, that the unspecific axons in cortex are the substrate for recruiting evoked in widespread areas and, therefore, arise from the nonspecific nuclei.

The differentiation between augmenting and recruiting responses became the basis for more than two decades of investigation. The augmenting response was evoked by repetitive low-frequency stimulation of the main sensory relay nuclei, among others, and was recorded only in restricted cortical areas whose loci varied with the thalamic site of stimulation (Morison and Dempsey, 1942; Dempsey and Morison, 1942b). A biphasic (positive-negative) "primary" response appeared upon the first stimulus presentation, was "augmented" by repetition, and then followed repetitive stimulation with short latencies.

In contrast, the monophasic (negative at the cortical surface) recruiting response was evoked by 6- to 12-Hz stimulation of intralaminar and certain adjacent thalamic nuclei (Fig. 1) and appeared over widespread cortical areas.

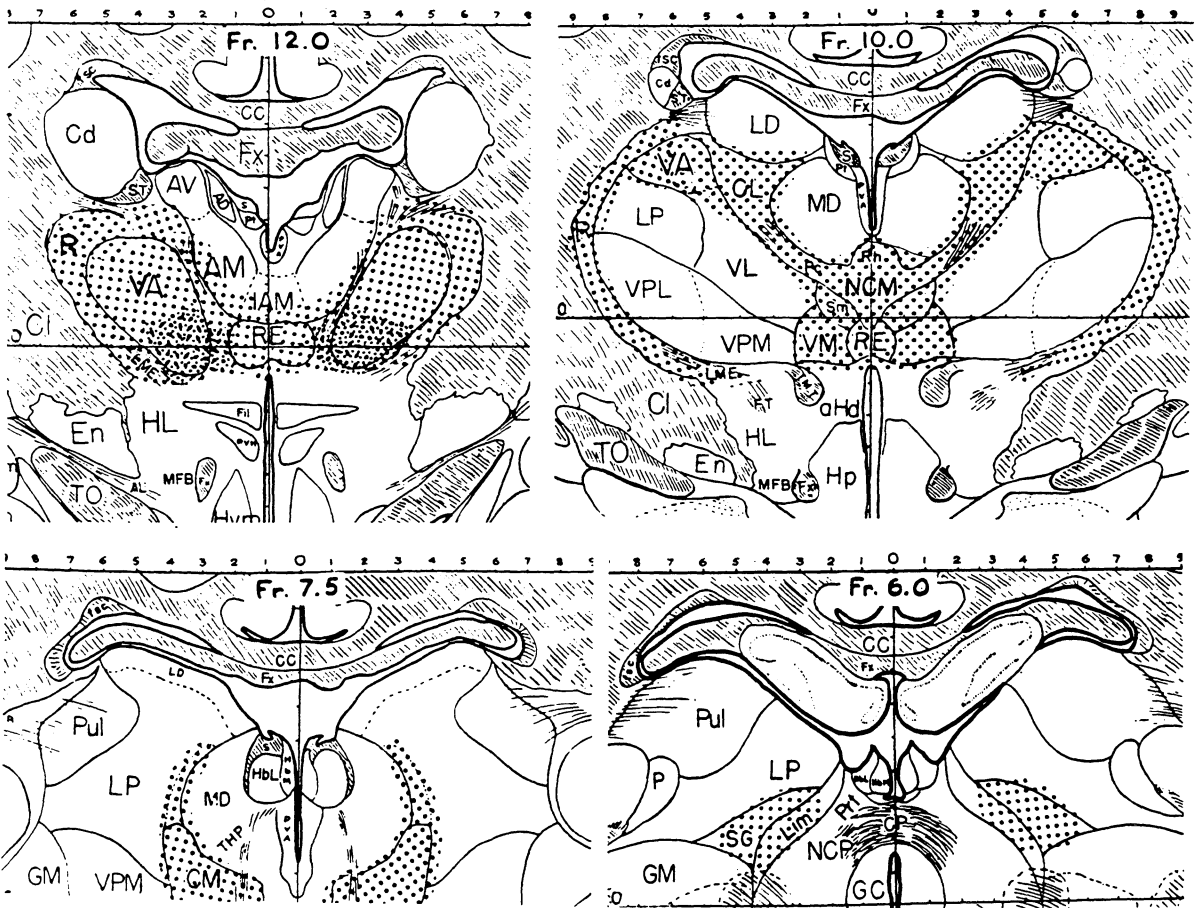


Figure 1. The location of the physiologically defined non-specific thalamus displayed at four coronal levels of the cat brain. Stipples mark sites where low-frequency (6–12 Hz) electrical stimulation produces recruiting responses in the cortex. The double stippling in medial VA (at Fr. 12.0) marks

the location where low-intensity stimulation elicits recruiting at widely dispersed cortical recording sites. Most of the abbreviations are given in the text. Reproduced with permission from Jasper (1961).

The response typically did not appear after the first shock but increased to maximum amplitude after about three stimulus presentations (hence the name recruiting) and showed long latencies (10–30 msec).

The thalamic nuclei which produced the recruiting phenomenon when stimulated were found to be clustered in and around the internal medullary lamina or at the rostral pole of the thalamus (Fig. 1). They included midline nuclei (reuniens, rhomboid, centralis medialis), the intralaminar nuclei (paracentral, central lateral, and, posteriorly, the parafascicular and centre median nuclei), the thalamic reticular nucleus (especially at the rostral pole), and nuclei adjacent to the internal medullary lamina (ventroanterior, ventromedial, submedius, paralamina parts of the mediodorsal and anteromedial, suprageniculate, and limitans). Because of widespread (diffuse) cortical responses to their stimulation, these nuclei were collectively termed the nonspecific thalamus.

The nonspecific thalamus attracted much attention because of its apparent functional significance as a potential center for controlling physiological and behavioral levels of arousal, and even consciousness itself. Penfield (1954) proposed the existence of a subcortical "centrencephalic" system capable of generating bilateral cortical wave-and-spike patterns in certain petit mal epilepsies. The additional observations that electrical alterations in different cortical areas often occur concurrently, and that the wave-and-spike pattern can be produced by nonspecific thalamic stimulation, supported the view of a thalamic pacemaker of cortical activity (reviewed in Krupp and Monnier, 1966). Furthermore, it was found that the cortical distribution, waveform properties, and waxing and waning of the amplitude of the recruiting response were similar to those of "spindles" emitted during a synchronous EEG state associated with drowsiness or inattention in animals (Morison and Dempsey, 1942; Phillips *et al.*, 1972). By contrast, when stimulated with high-frequency pulses (>60 Hz), the nonspecific nuclei could also produce widespread desynchronization of cortical activity (Dempsey and Morison, 1942a; Moruzzi and Magoun, 1949), an EEG state associated with arousal and vigilance (Steriade, 1981).

Although the initial observations suggested a promising future for studies of nonspecific thalamocortical function, subsequent research failed to reveal those functional bases. As anatomical and physiological scrutiny grew more intense, the hypothesis that all nonspecific nuclei had connectional and functional similarities became untenable. For example, it was discovered that the thalamic reticular nucleus does not project to cortex at all (Scheibel and Scheibel, 1966; Jones, 1975b) and that stimulation of the ventroanterior or ventrolateral nuclei, but not of certain other nuclei, evoked both augmenting and recruiting responses in different cortical regions (Jasper, 1961; Sasaki *et al.*, 1970). Even the dichotomy of augmenting and recruiting was questioned (Schlag and Villablanca, 1967). Gradually, the focus of research was shifted to other areas. Nowadays, many researchers consider the nonspecific thalamus to be just a vague construct.

Hopefully, however, a number of recent anatomical findings may rekindle an interest in nonspecific thalamocortical organization and function. Although new physiological data are scarce, a wealth of relevant connectional data from axoplasmic transport studies has accumulated in the past decade. The remainder of this chapter will be devoted to a presentation and review of the anatomical bases for thalamocortical organization. A new organizational scheme will be presented which does not conform to the earlier two-part division of the thalamus

but which does help to resolve the aforementioned difficulties with the simple dichotomy of specific and nonspecific systems.

Anatomical evidence to be presented in this chapter introduces a tripartite grouping of thalamic nuclei. The grouping is based on the lamination patterns of thalamic axons in rat cortex. The laminar patterns will be correlated with other features of axon distributions (e.g., restricted versus widespread), and they will be discussed from functional and comparative points of view.

2. A Tripartite Division of Thalamus Based on Cortical Layers of Termination

A scheme that has proven useful for classifying thalamic nuclei is based on the lamination patterns of their cortical projections in the rat (Herkenham, 1980a,b). The lamination patterns can be grouped into three classes; hence, so can the thalamic nuclei of origin. One class, which contains the specific nuclei, is well known. Details of the second and third classes have often been confused; the present clarification is based on studies employing the anterograde flow of tritiated amino acids in the rat. These data appear in several publications (Herkenham, 1978b, 1979, 1980a) and in this chapter. See also the chapters by Jones and White in this volume and others in Volumes 3 and 4 of this treatise.

The first class includes the thalamic relay nuclei for vision, audition, and somesthesia. The cortical projections terminate mainly in layer IV, layer III, or both. The fibers in this class correspond to the traditionally defined specific cortical afferent fibers (Lorente de Nó, 1938). The second class includes the intralaminar and thalamic paraventricular nuclei, which project to deep cortical layers (layer V, VI, or both). The third class comprises an assortment of nuclei that share a pattern of dense, widespread projections to layer I, though terminations in other layers may or may not be present. These layer I-projecting nuclei generally occupy a position adjacent to the intralaminar nuclei. Hence, they also will be referred to as the "paralaminar" nuclei, a term previously used to denote only portions of the present collection comprising the third class (Nauta and Whitlock, 1954; Rieck and Carey, 1982b,c). The three classes of nuclei are illustrated in Fig. 2.

Although the classification scheme is based on laminar distribution patterns, it is noteworthy that the projections of the first class have restricted areal extents, whereas those of the second and third classes appear to span widespread areas of cortex. Therefore, the areal distributions of fibers of the second and third classes make both classes likely candidates for inclusion in the physiologically defined nonspecific thalamus. The match is not perfect, however. The nonspecific nuclei of the earlier, physiological scheme (Fig. 1) include the following nuclei of the present, anatomical scheme (Fig. 2): the paralaminar mediodorsal nucleus of the first class, the intralaminar nuclei of the second class, and several paralaminar nuclei of the third class. The reticular nucleus, an important component of the physiologically defined nonspecific thalamus, is not included in any of the three current classes because it lacks cortical projections.

The remainder of Section 2 will provide anatomical details of the tripartite organization of the rat thalamus. Most of the focus of this section and the

remainder of the chapter will be on the third class of fibers, the layer I-projecting class, for several reasons. First, the initial description of the “unspecific” fiber type in cortex by Lorente de Nó (1938) indicated that layer I was the predominant layer of termination of the putative diffuse thalamic projection system. Closely tied to this point is the second point, that the recruiting response was commonly believed to be generated by synaptic events occurring initially in layer I (Li *et al.*, 1956; Spencer and Brookhart, 1961). Third, a major goal of this chapter is to dispel a generally held view that the intralaminar system is the main thalamic origin of layer I projections, presenting anatomical evidence for the distinction between intralaminar (deep layer projecting) and paralaminar (layer I projecting) nuclei, and then arguing that these two systems might contribute to cortical function, particularly in relation to the recruiting response and diffuse thalamocortical physiology.

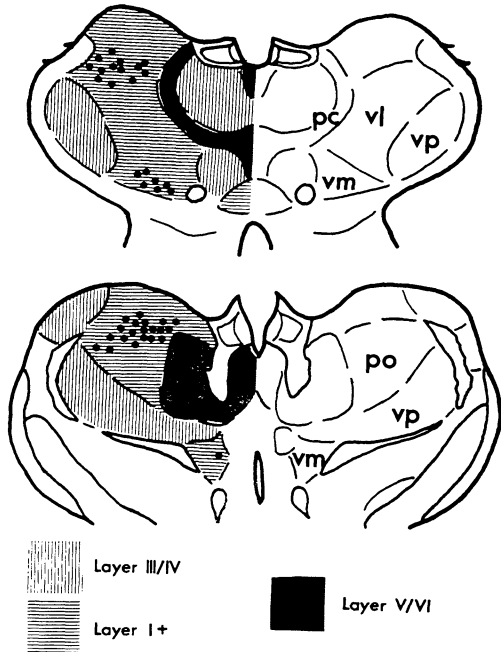
2.1. Specific Nuclei

Characteristics of the nuclei of origin and the dense arborizations of specific thalamocortical fibers in layers III/IV have been described in detail elsewhere (see White, this volume) and will not be discussed here.

2.2. Nonspecific Deep Layer-Projecting Nuclei

Fibers of the second class project mainly to deep cortical layers. Intralaminar nuclei are the main source of these fibers in the rat. The intralaminar system is

Figure 2. Drawings of two thalamic levels in the rat, showing a tripartite division based on the laminar patterns of terminations of thalamocortical projections. Hatched and shaded areas mark nuclei which have been shown by autoradiography of anterogradely transported tritiated amino acids to have projections directed predominantly to superficial, intermediate, or deep cortical layers. The black dots show the locations of retrogradely labeled neurons in a case in which HRP was infused into layer I of somatosensory cortex (Herkenham and Moon Edley, unpublished). Note that the cells are found only in areas that project to layer I according to the autoradiography. pc, paracentral; po, posterior; vl, ventrolateral; vm, ventromedial; vp, ventroposterior nuclei. Reproduced from Herkenham (1980b).



the subject of Macchi and Bentivoglio's contribution in this volume and so only the salient features will be presented here.

2.2.1. Intralaminar Efferents

Tritiated amino acids, iontophoretically delivered in very small amounts to the intralaminar (central lateral, paracentral, central medial), parafascicular, and paraventricular nuclei in the rat, label sparse but widespread projections to deep layers of neocortex. Two examples will illustrate the general features of this system. The central medial nucleus (CeM) is a relatively large, cytoarchitecturally distinct nucleus, making possible a relatively confined injection (Figs. 3d, 4).

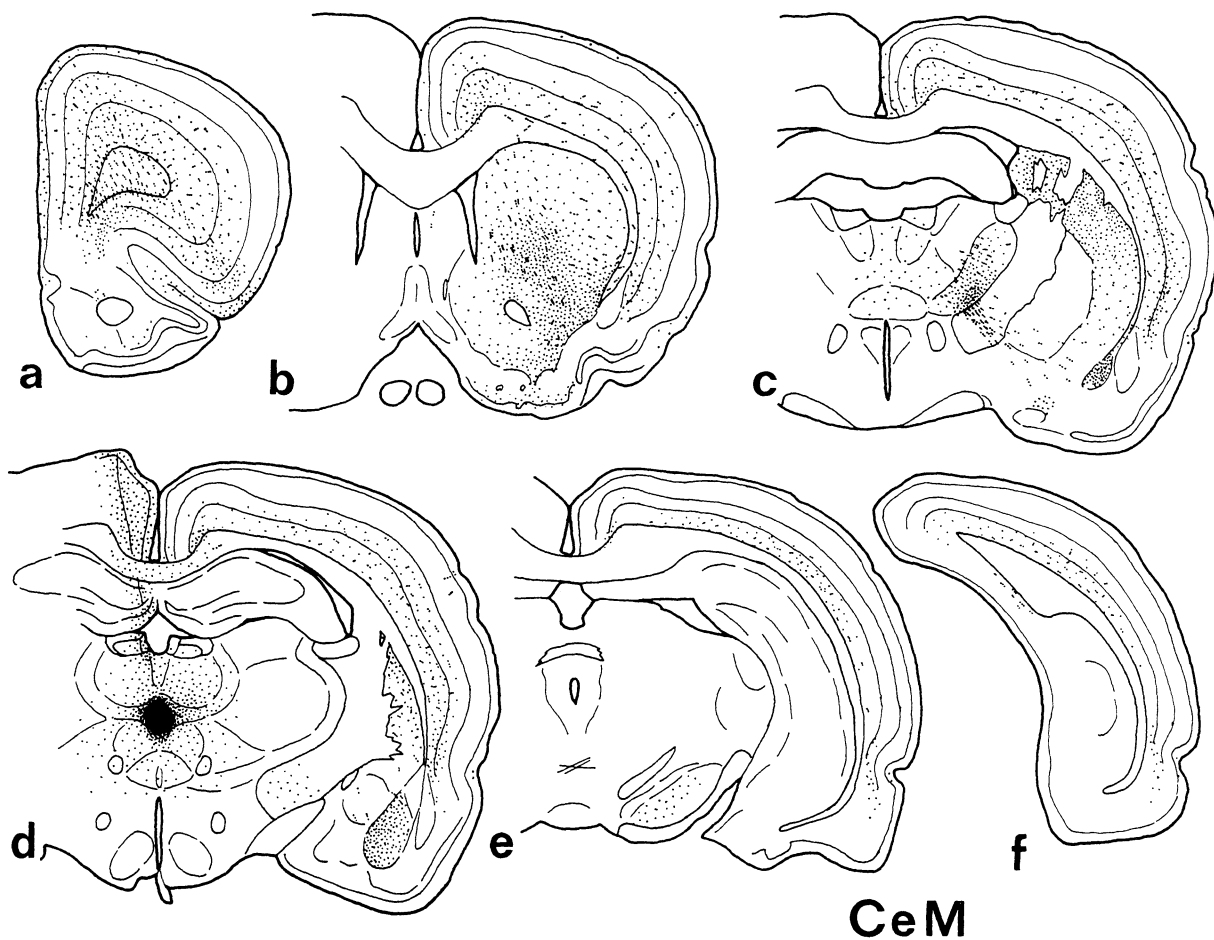


Figure 3. Drawings of coronal levels in the rat, showing distribution of labeled fibers arising from the midline intralaminar nucleus, CeM (central medial nucleus). Labeled fibers and terminals are represented by small dots arranged to resemble how they appeared under microscopic examination. The main projection targets are the cau-

date-putamen (b-d) and layers V and VI of nearly the entire cerebral cortex. In this and subsequent drawings, solid lines in the cortex indicate the layer I/II boundary and the upper and lower boundaries of layer V. Details of this projection are given in the text. Case RRCeM-13, 18 weeks' exposure to the emulsion.

Tracer placed rostrally in CeM labels projections to layer V and/or VI in virtually the entire cerebral cortex (Fig. 3). Labeled CeM axons pass through the ventorostral part of the reticular nucleus and issue collaterals that terminate densely there (Fig. 3c). Most axons reach the striatum, in which they terminate or enter the subcortical white matter and deep layers of cortex (Fig. 3b,c). CeM fibers in frontal cortex terminate in layers V and VI (Fig. 3a). A small number of fibers ascends to layer I of the medial frontal and sulcal areas (Fig. 3a). In parietal (Figs. 3b–d, 4) and occipital (Fig. 3e,f) areas, labeled fibers run long distances within layer VI.

Injections placed elsewhere in the intralaminar complex reveal projections with more limited areal extents. Figure 4 shows the sparse distribution of labeled fibers in layers V and VI of parietal cortex after a small deposit was placed in the paracentral (Pc) nucleus. Further details of the distributions and topography of intralaminar projections have been summarized (Herkenham, 1978a, 1980a).

2.3. Nonspecific Layer I-Projecting Nuclei: The Paralaminar System

The third class of thalamocortical axons arises from five to ten nuclei in the rat, depending on whether nuclei with projections to juxtallocortical structures are included. Most of these nuclei are paralaminar in location, but their cardinal feature is that they all have in common a dense projection to layer I. There is no representative member of this class because most nuclei project additionally to other cortical layers. The designation “Layer I+” in Fig. 2 refers to the fact that additional layers of termination exist. Since the laminar positions of additional terminations vary, depending on the cortical area in which they are found, these nuclei are said to show “area-dependent lamination” (Herkenham, 1980a). The nuclei will be presented in the approximate order that they appear in the thalamus from rostral to caudal.

2.3.1. The Reuniens (Re) Nucleus

Re projects to layer I of limbic cortex spanning the entire rostrocaudal extent of the brain (Herkenham, 1978b). Amino acid-labeled Re projections reach prelimbic and infralimbic areas of frontal cortex, cingulate and retrosplenial areas, and the hippocampus, subiculum, and entorhinal cortex (Fig. 5). In all of the innervated areas the terminations are dense in layer I (which in the hippocampus is the stratum lacunosum-moleculare). Area-dependent lamination is also observed, as the entorhinal area has additional terminations in layer III (Fig. 5). The cells of origin of this projection have been localized to Re by the results of studies in which HRP was deposited into the prelimbic and cingulate areas (Beckstead, 1976), entorhinal cortex (Beckstead, 1978), and hippocampus (Wyss *et al.*, 1979).

2.3.2. The Anterior and Lateral Dorsal Nuclei

Four nuclei other than Re project to layer I of medial limbic cortex. They include the anteromedial (AM), anteroventral (AV), and anterodorsal (AD) nu-

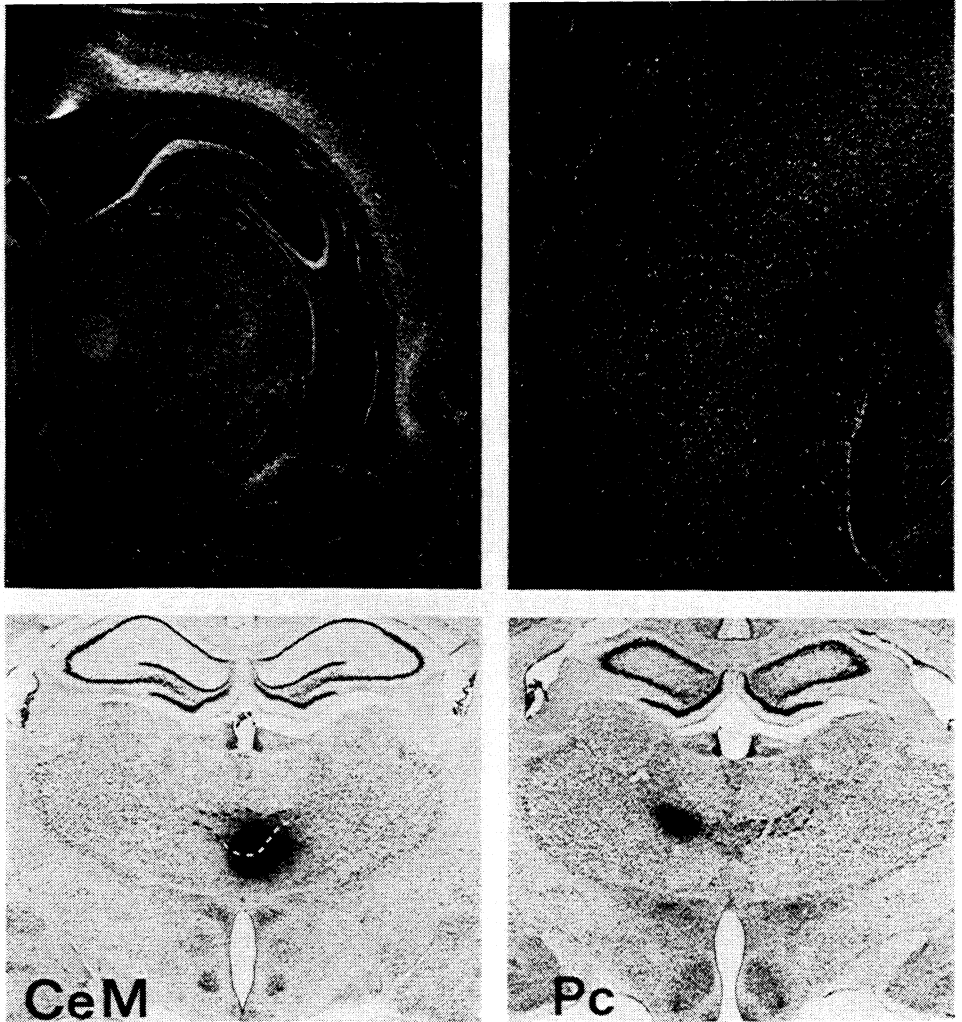


Figure 4. The intralaminar nuclei. Photographs of two cases of tritiated amino acid uptake (lower) and transport (upper), shown in brightfield and darkfield illumination, respectively. The boundaries of the intralaminar nuclei are marked by the dashed lines in the lower photographs. (Left) Case RRCEm-17, 30 weeks' exposure; injection of rostral CeM and adjacent nuclei shown at bottom; at top, a level between those of Fig. 3d and 3e shows labeled fibers in deep cortical layers. The hippocampal labeling results from involvement of reuniens nucleus (compare Fig. 5). (Right) Case RRPc-8, 20 weeks' exposure; injection nearly confined to the paracentral (Pc) nucleus shown at bottom; at top, a higher magnification view of parietal cortex overlying the fimbria at about the same level as the injection site. The labeled fibers in layers V and VI are represented by tiny, sparse silver grains dispersed over the less reflective neuropil.

clei of the anterior group, and the lateral dorsal (LD) nucleus. Each nucleus has a preferred cortical target and projects to layers in addition to I. For example, as shown in Fig. 5, LD projects to layer I of both granular and agranular retrosplenial areas, but also to layer III/IV of the agranular cortex. LD also projects in bilaminar fashion to the presubiculum (note this pattern in Fig. 6). Interestingly, the projections of LD and the anterior nuclei are to the same medial juxtallocortical territory innervated also by Re (Herkenham, 1978b). Yet the

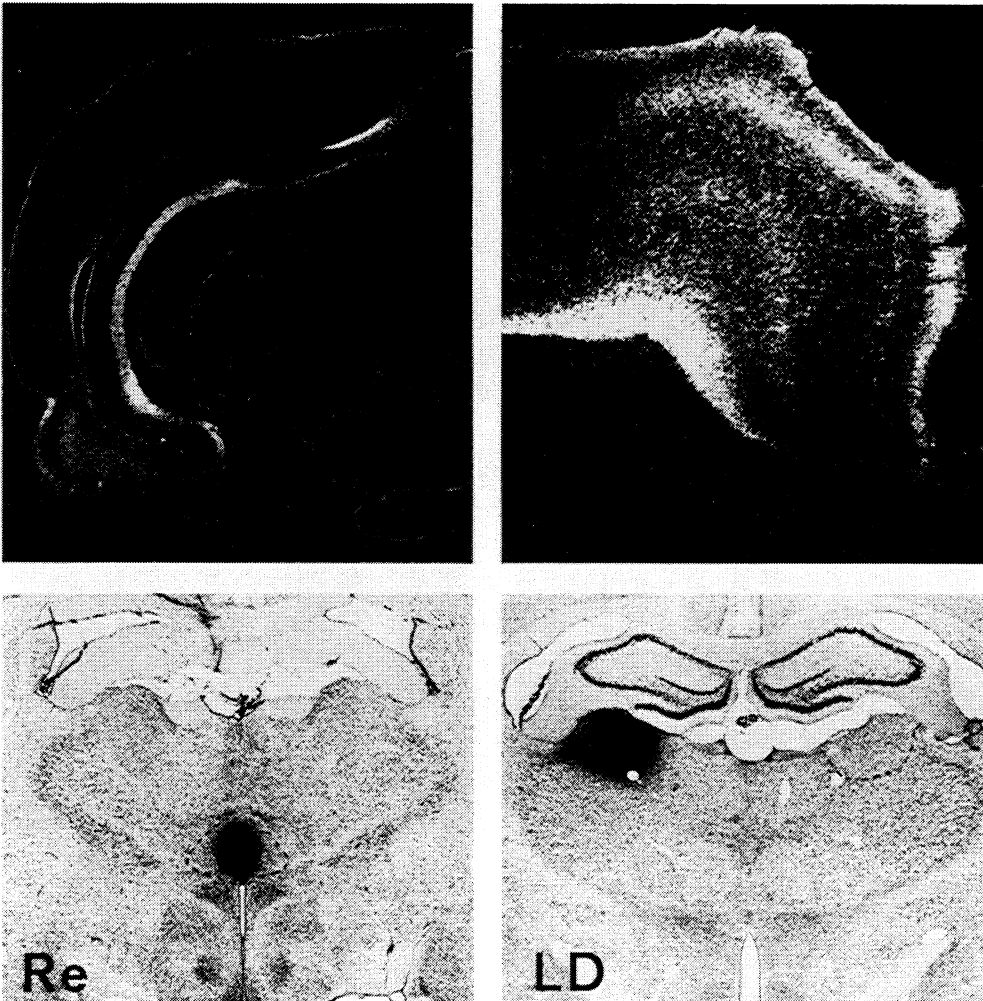


Figure 5. Paralaminar nuclei with projections to layer I of limbic cortical areas. The boundaries of the injected nuclei are depicted by dashed lines in the lower photographs. (Left) Case RRCeM-4, 20 weeks' exposure; at bottom, injection of reuniens (Re) nucleus; at top, resultant labeling of stratum lacunosum/moleculare of hippocampal field CA1, as well as layer I of parahippocampal fields and layers I and III of entorhinal cortex. Fibers enter from the cingulate bundle dorsally. (Right) Case RRLT-2, 15 weeks' exposure; at bottom, injection of the lateral dorsal (LD) nucleus; at top, labeling in the cingulate bundle (lower left), layer I of granular retrosplenial (right) and layers I and IV of agranular retrosplenial (upper right) areas. This is an example of area-dependent lamination.

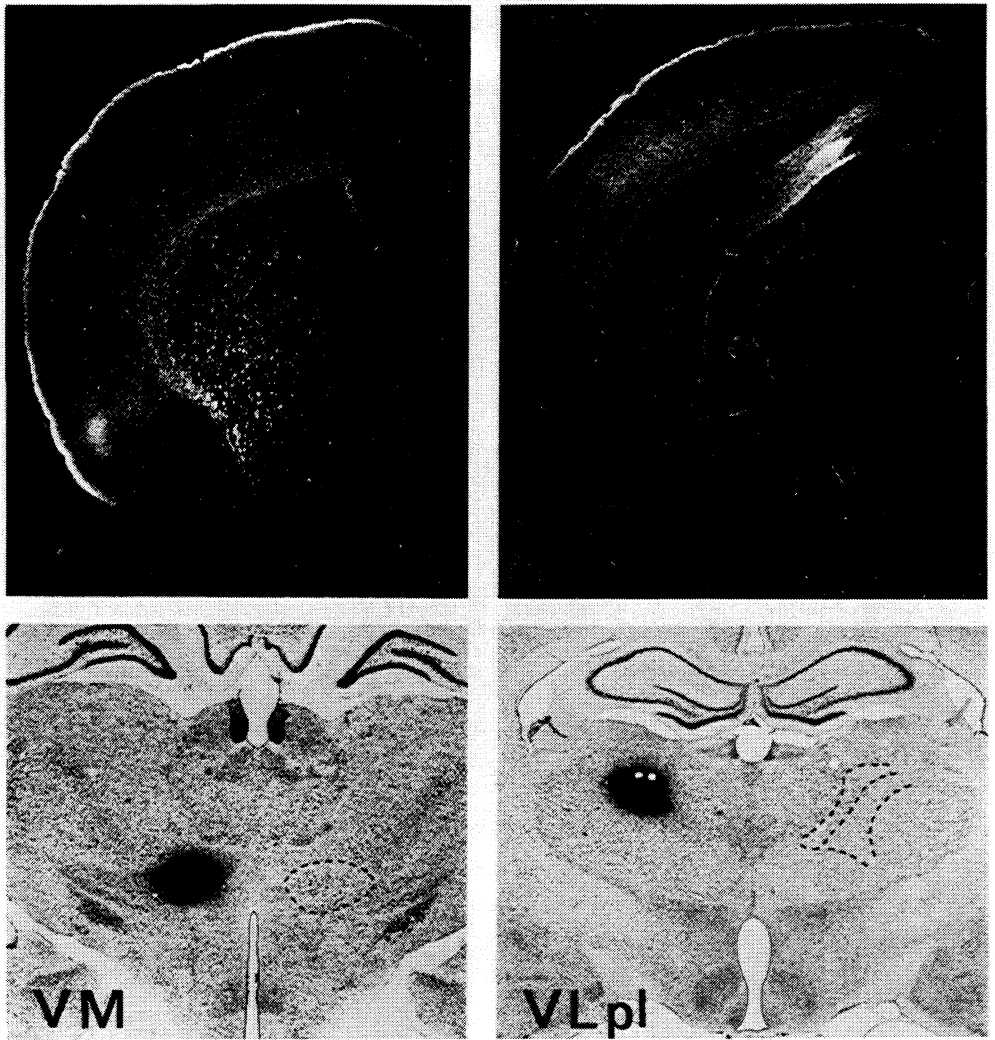


Figure 6. Paralaminar nuclei of the ventral complex with projections to layer I of nearly the entire neocortex. Boundaries of the injected nuclei drawn on the contralateral side. (Left) Case RRVM-11, 16 weeks' exposure; at bottom, injection of the ventromedial (VM) nucleus, which has projections that terminate nearly exclusively in layer I of frontal and parietal cortex, as shown at top. The small patch of label in layer IV of far-lateral cortex results from transport from the thalamic taste relay nucleus just dorsal to VM. (Right) Case RRCL-7, 17 weeks' exposure; at bottom, the location of the ventrolateral (VL) complex is outlined. VL is further subdivided into a medial, paralaminar part (VLpl) and a lateral part as described in the text. The projections in this case are charted in Fig. 7. The dense VLpl projections to layer I and V/VI of occipital cortex are seen at the top. The uptake of label by cells dorsally, in LD, resulted in transport to the presubiculum shown at the top and in Fig. 7g.

areas of greatest termination density are complementary; Re projects very sparsely to those areas where LD and the anterior nuclei project most densely. These relationships have been described in more detail elsewhere (Domesick, 1972; Herkenham, 1980a).

2.3.3. The Ventromedial (VM) Nucleus

VM is a clearly demarcated nucleus which receives nigrothalamic fibers (Herkenham, 1979). VM is the quintessential nonspecific thalamic nucleus in the rat, as it appears to be the only one with cortical projections that terminate almost exclusively in layer I (Fig. 6). Furthermore, its terminations in layer I cover a cortical expanse nearly as great as that covered by the intralaminar projections shown in Fig. 3. The discovery that VM is the source of widespread layer I connections (Leonard, 1969; Krettek and Price, 1977; Herkenham, 1979) is significant in light of findings that in the cat, the rostral VM and ventromedial portions of the ventroanterior (VA) nucleus are focal points for eliciting recruiting responses in cortex (see Fig. 1) and may represent the "final paths" for thalamocortical recruiting waves recorded in layer I (Herkenham, 1979; Glenn *et al.*, 1982; see also Section 4.2.1.).

2.3.4. The Paralaminar Ventrolateral (VLpl) Complex

In the rat there are no clear cytoarchitectural distinctions to permit localization of distinct subdivisions within the VA–VL complex. Hence, the cerebellar-recipient part of the ventral complex, outside VM, has been called the ventrolateral (VL) complex (Donoghue *et al.*, 1979). The medial part of VL is the source of projections that extend beyond the confines of motor cortex; here it is designated paralaminar VL (VLpl) because of its proximity to the internal medullary lamina (Fig. 6). Injections placed in lateral parts of VL label projections confined to frontal cortex (not shown). In contrast, amino acids placed in VLpl label fibers in layer I in the frontal, parietal, and occipital areas (Fig. 7).

The projections of VLpl show area-dependent lamination patterns: in the agranular frontal area (primary motor cortex, MI) they are localized in layer I, layer III, and a band straddling the border of layers V and VI (Fig. 7a,b); in the granular parietal areas (primary somatosensory cortex, SI) they appear in layers I and VI, and in visual cortex (both area 17 and area 18) terminations appear in layer I and throughout a broad zone including layers V and upper VI (Figs. 6, 7f–h).

The pattern of dense VLpl fiber termination in layer I of occipital cortex complements the pattern of dense layer I projections of VM in frontal cortex. Therefore, the two paralaminar components of the ventral complex, VM and VLpl, together provide dense layer I projections to all of the rat neocortex except the temporal auditory area.

2.3.5. The Posterior (Po) Nucleus

Amino acids injected into Po mark topographically organized (Herkenham, 1980a) but widespread projections to layer I of the somatosensory and motor

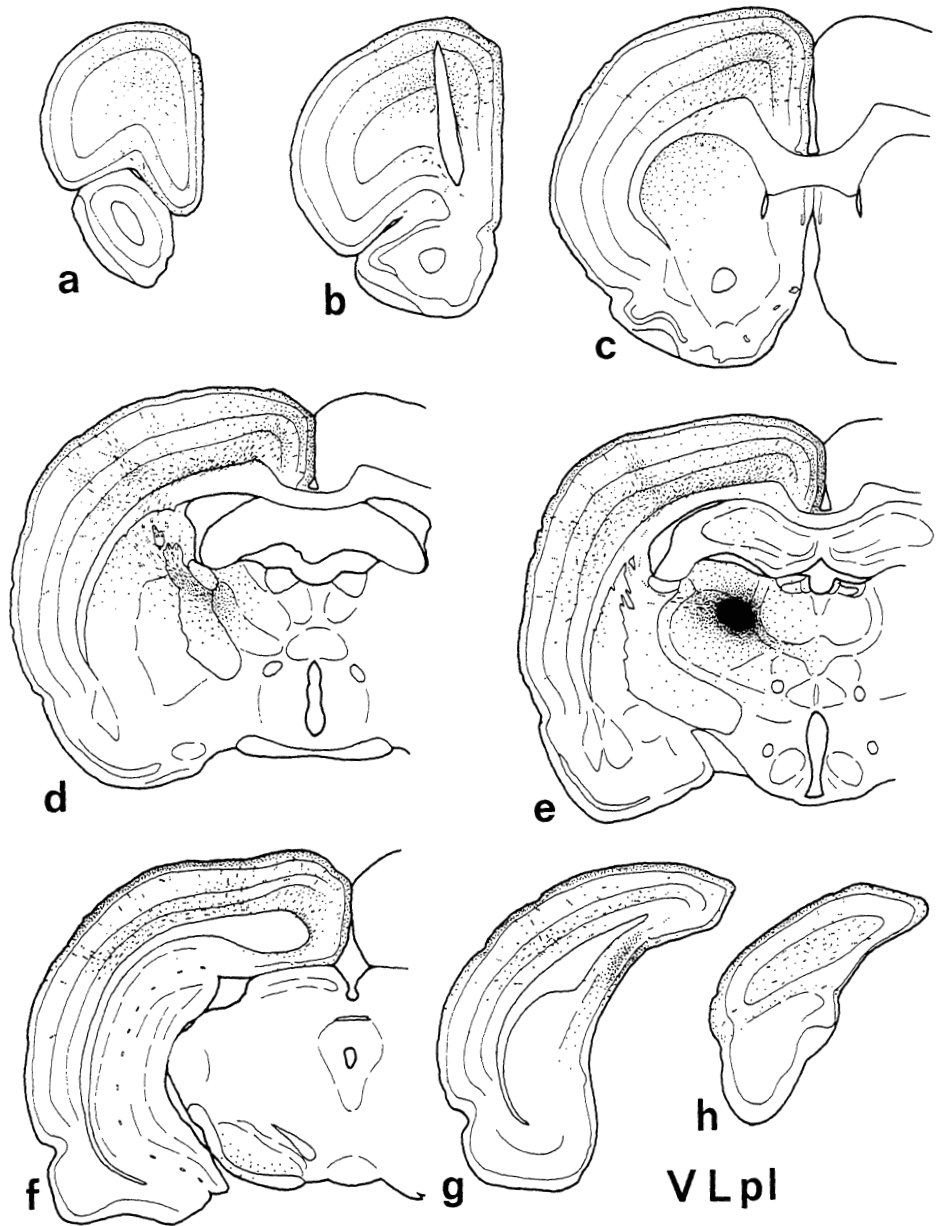


Figure 7. Drawings of ^3H -amino acid-labeled projections of the paralamina of the ventrolateral complex (VLpl). Case RRCL-7, also shown in Fig. 6. Details are given in the text.

areas of parietal and frontal cortices (Figs. 8, 9). The Po projections show area-dependent lamination patterns, as follows. In the agranular motor areas, terminations are located in layers I and III (Fig. 9a). In SI cortex containing a dense granular layer IV (koniocortex), terminations are in layers I, upper V, and VI (Fig. 9a-d). In dysgranular portions of SI, sprays of label represent fibers terminating in layer IV and ascending to layer I (see also Fig. 5 of Lewis *et al.*,

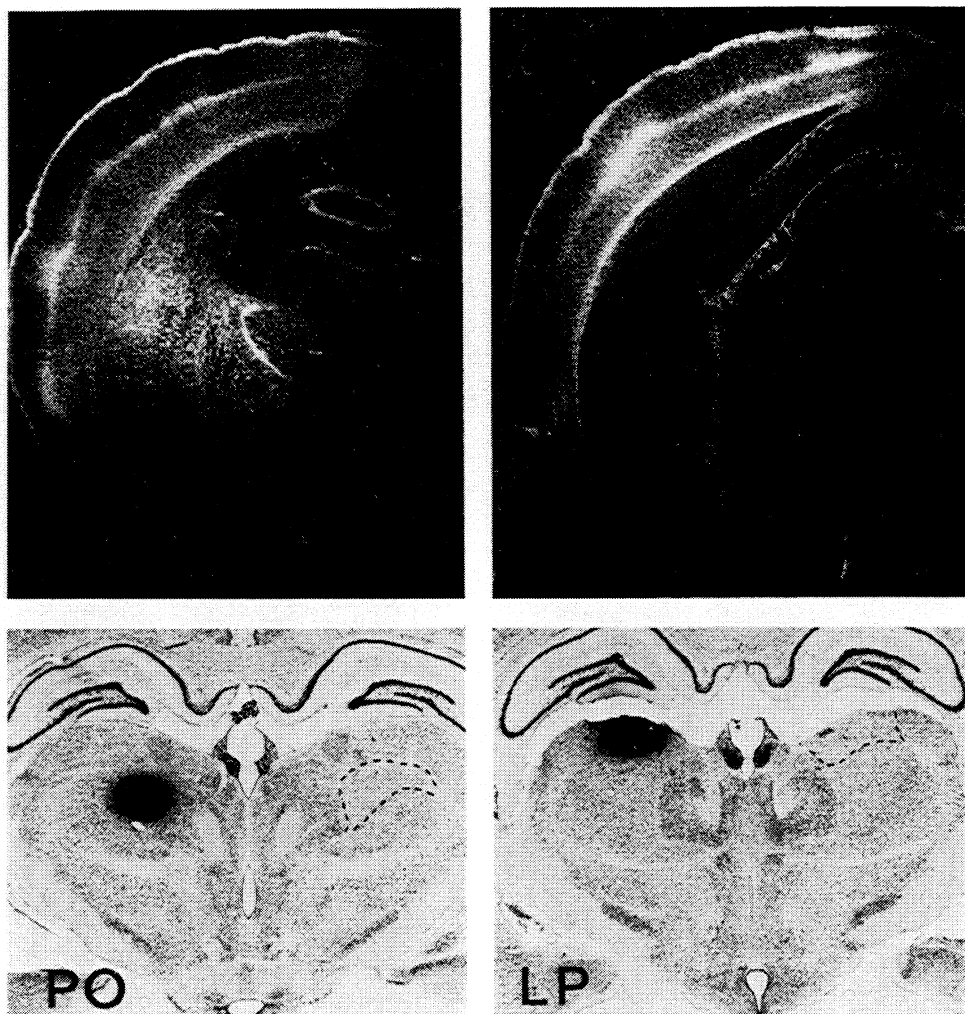
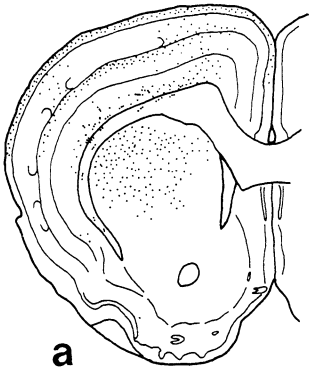
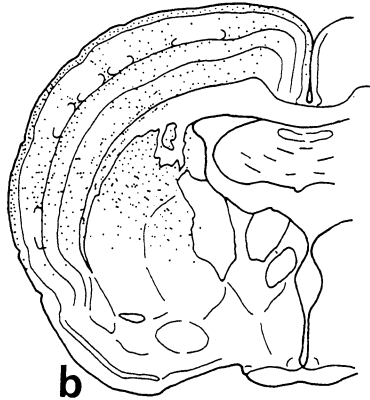


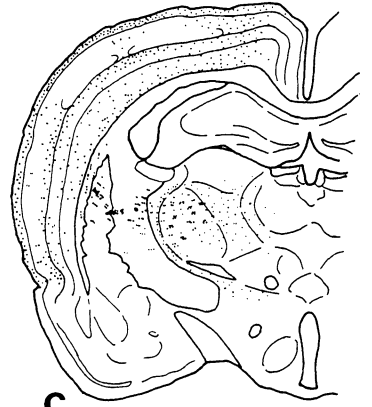
Figure 8. Photographic documentation of paralamina nuclei projecting with area-dependent lamination to "layer I+" of the somatosensory and visual fields, as described in the text. (Left) Case RRPc-13, 24 weeks' exposure; at bottom, injection of the somatosensory portion of the posterior (PO) complex, outlined on the contralateral side. The darkfield photograph shows area-dependent lamination patterns: terminations are in layers I and Va in granular cortex and in layers I and IV of dysgranular, or homotypical, parietal cortex. (Right) Case RRLT-5, 29 weeks' exposure; at bottom, injection to the lateral posterior (LP) nucleus; at top, projection to visual cortex. The darkfield photograph shows terminations in layers I and V of area 17 flanked on both sides by terminations in layers I and IV of area 18.



a

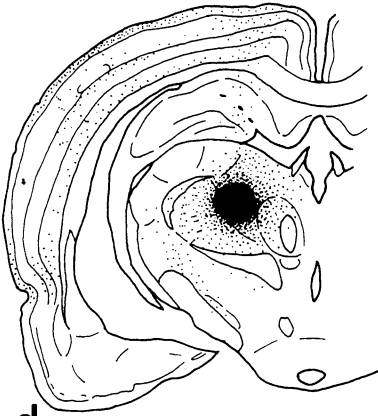


b



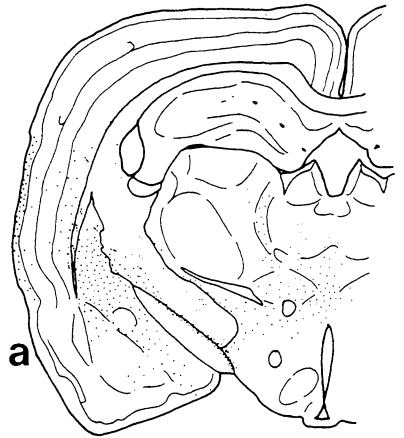
c

PO



d

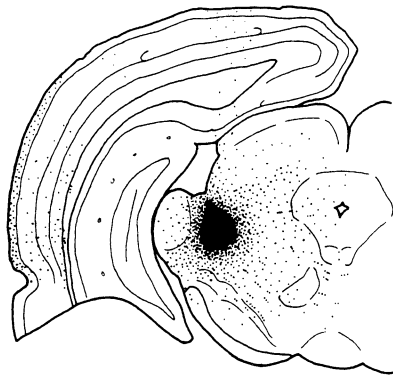
MGm



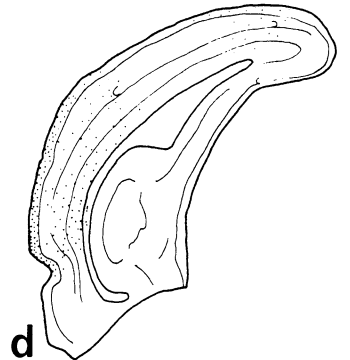
a



b



c



d

1983). Throughout the parietal homotypical cortex, terminations appear in layers I and IV.

Confirmation that Po neurons are the source of layer I projections to SI is shown by the results of experiments summarized in Fig. 2. The dots show where retrogradely labeled cells were found in Po but not in the ventroposterior (VP) nucleus (first class) or in the intralaminar nuclei (second class) after HRP was injected into the outer two layers of SI. In the rat several other studies show retrograde cell labeling in Po after HRP was injected into motor (Donoghue and Parham, 1983) and somatosensory areas (Donoghue *et al.*, 1979). These studies confirm the wide areal distribution of Po fibers, but do not address their lamination pattern.

2.3.6. The Lateral Posterior (LP) Nucleus

Because LP is considered to be a main relay to middle layers of nonprimary visual cortex, the inclusion in the layer I-projecting class may seem curious. In fact, LP is a nucleus which projects with area-dependent lamination. Autoradiographic analyses show that LP projects densely to layer IV of area 18 (Hughes, 1977; Herkenham, 1980a). However, it also projects densely to layer I of area 18. This feature by itself does not qualify LP for inclusion in the layer I-projecting system since other specific nuclei also project densely to layer I, notably the mediodorsal (MD) nucleus (Leonard, 1969; Krettek and Price, 1977). A major distinction between the projections of LP and MD is that MD projections terminate in the same laminar pattern throughout the extent of their cortical distribution, whereas LP projections show area-dependent lamination patterns. Thus, LP projects to layers I and IV of area 18 but to I and V of area 17 (Fig. 8). Moreover, amino acids placed in different parts of LP label projections with variable terminal patterns—in some cases termination in layer I is denser than in layer IV and in others not only is that relationship reversed but also the projection to area 17 is sparse (unpublished data). More work is obviously needed, but it appears that in the rat, as in many other species, LP has subdivisions, some of which may be more specific in their connections and others more nonspecific. The inclusion of the entire nucleus in the layer I system in the schematic drawing in Fig. 2 should be treated as a convenient simplification. The same can be said for the representation of VL in Fig. 2.

2.3.7. The Magnocellular Medial Geniculate (MGm) Nucleus

None of the layer I-projecting nuclei discussed thus far sends fibers to the portion of temporal cortex which contains the auditory fields. The MGm and adjacent suprageniculate (SG) nuclei provide projections to layer I of this lat-

←
Figure 9. Drawings of projections of the somatosensory portion of the posterior (PO) complex. Case RRPc-13, shown also in Fig. 8. The terminations in layer I span the somatosensory field, as described in the text.

Figure 10. Drawings of projections of the magnocellular medial geniculate (MGm) nucleus. Case RRMG-8, 38 weeks' exposure, injection of the reticular formation and caudal MGm, without involvement of other parts of the medial geniculate complex. The layer I termination spans the auditory field, as described in the text.

eralmost cortex. In the case charted (Fig. 10) the amino acids were taken up and transported by neurons in caudal MGm but not by neurons in the adjacent main relay portion of the medial geniculate complex. Consequently, projections to layer IV are not evident anywhere in the cortex; rather, grains throughout the depths of the cortex are arranged in patterns that indicate fibers terminating in layer I and the infragranular layers (Fig. 11).

The SG has a major projection to layers I and V/VI of the same wide extent

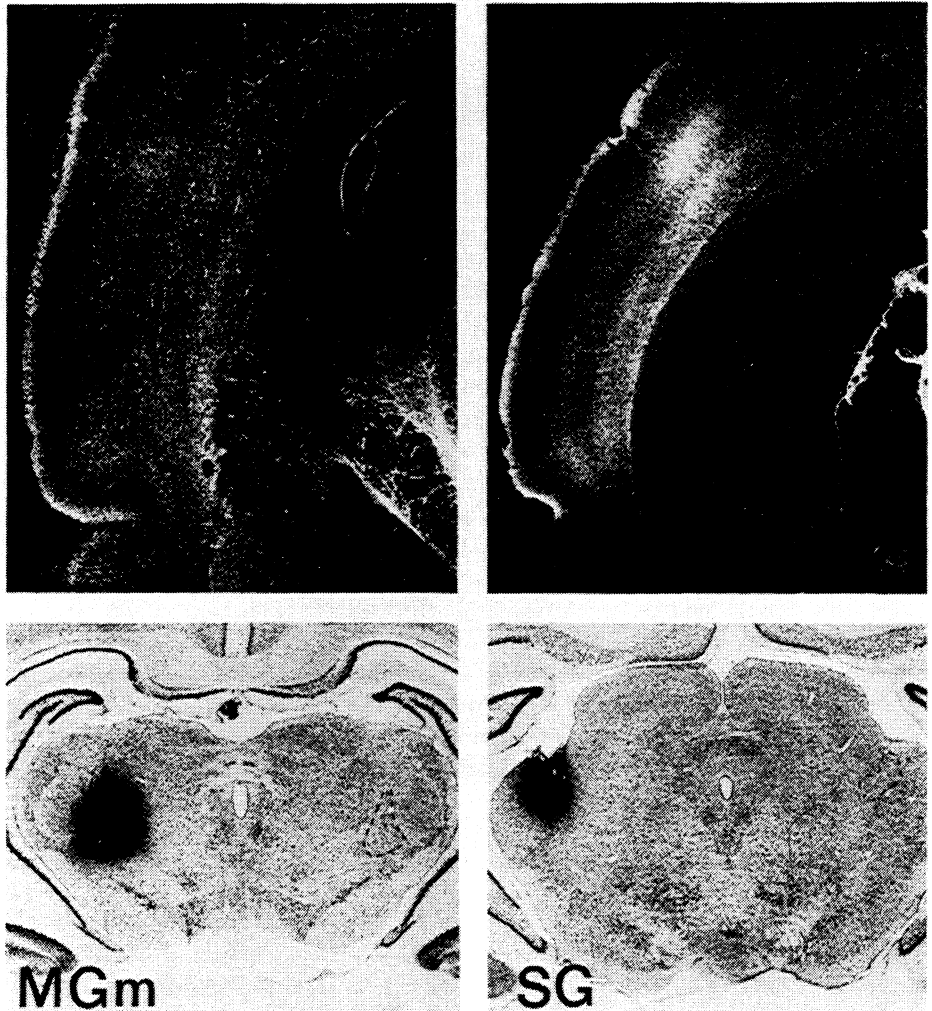


Figure 11. Layer I-projecting nuclei of the auditory system (Left) Case RRMG-11, 41 weeks' exposure; at bottom, large injection with the magnocellular medial geniculate (MGm) nucleus at its center. The darkfield photograph shows a rostral level of auditory cortex at the level of amygdala, similar to that in Fig. 10a. Terminations are densest in layers I and VI. (Right) Case RRMG-15, 37 weeks' exposure; at bottom, injection with its center at the suprageniculate (SG) nucleus, which is outlined on the contralateral side. The darkfield photograph shows a posterior level of auditory cortex, similar to that shown in Fig. 10d. Terminations are in layers I and VI. The patch of dense label in layer IV at the dorsal part of auditory cortex probably arises from label uptake by neurons in the principal portion of the MG complex.

of the auditory areas as does MGm (Fig. 11). Further studies are required to determine whether terminations in layer IV in this case arise from cells in SG or in the adjacent principal MG.

The lamination pattern of MGm projections to rat auditory cortex was originally described by Ryugo and Killackey (1974) on the basis of silver stains of degenerating axons. The material in that study shows sparse degenerating axons ascending to and running in layer I. By comparison, the same projection labeled autoradiographically shows a greater relative proportion of axons reaching layer I (Fig. 11), probably demonstrating the greater sensitivity of the autoradiographic method.

3. Evidence for a Paralaminar Layer I-Projecting System Demonstrated by Retrograde Tracing

The cells of origin of superficial and deep projections have been identified by retrograde transport of HRP from superficial or deep cortical injection loci. HRP restricted to layer I of rat visual cortex labels neurons in a rostral thalamic paralaminar strip comprising VM, VLpl, and, more rostrally, the rostral pole region, which has been called VA (Rieck and Carey, 1982c). A similar labeling pattern results from HRP injections into layer I of the primary somatosensory or motor areas, though cells in Po are also labeled (Fig. 2; Rieck and Carey, 1982b). More importantly, in none of these cases are intralaminar neurons labeled. However, when HRP is injected into layers III–VI of visual cortex, cells are labeled within nuclei of all three divisions of the tripartite thalamus (Carey and Neal, 1982).

Some very exciting results are presented in a recent study in which D- ^3H aspartate was injected into superficial or deep regions of somatosensory or motor cortex (Ottersen *et al.*, 1983). The labeling patterns in the nonspecific nuclei resemble those found with HRP injections: the superficial injections primarily label neurons in VL, VM, and Po, and the deep injections label intralaminar neurons in greater numbers. The striking difference between aspartate and HRP, however, is that the putative amino acid transmitter is not retrogradely transported to neurons in the specific relay nuclei (Ottersen *et al.*, 1983). The results suggest that the neurotransmitter for the two classes of nonspecific nuclei is either glutamate or aspartate. This conclusion is very tentative, as no thalamocortical transmitter has been identified with any level of confidence. The selective labeling should serve as a stimulus for future studies of the differential neurochemistry of the specific and nonspecific systems.

4. Comparative Aspects of the Nonspecific Thalamocortical System

4.1. Generalized Mammals

While the nonspecific thalamus as a physiologically defined entity has been extensively studied only in cats, and less so in monkeys, much of the anatomical

basis for the system comes from efforts to identify widespread thalamocortical connections in opossums, hedgehogs, tree shrews, and bushbabies. Because they appear to retain generalized ancestral features, these animals have been chosen for study in an effort by several groups to better understand brain organization from an evolutionary perspective. Thalamic phylogeny will be the subject of Section 6. The goal of this section is to provide evidence for the generality of the tripartite model of thalamocortical organization.

4.1.1. The Central Intralaminar Nucleus (CIN) Is Really Po

The first experimental demonstration of a thalamocortical projection terminating in the manner described by Lorente de N6 (1938) as "unspecific" was made by Killackey and Ebner (1972, 1973). Lesions of a posterior site in the opossum thalamus produced degenerating fibers in parietal cortex that ascend to layer I and terminate densely there. This landmark demonstration actually set back our understanding of thalamocortical organization for the single reason that the name given to the region giving rise to this projection was the central intralaminar nucleus (CIN), suggesting that it was part of the intralaminar system. Though CIN is clearly lateral to the internal medullary lamina, the homology of CIN in the opossum with Po in other species was not appreciated until very recently (Donoghue and Ebner, 1981; Neylon and Haight, 1983). CIN has cytoarchitecture and afferent and efferent connections similar to Po in other species; thus, it now appears that the opossum CIN is the homologue of the somatosensory portion of Po in those species (Donoghue and Ebner, 1981; Neylon and Haight, 1983). This is a critical fact for the tripartite scheme of thalamic organization because it supports the contention that dense layer I projections arise from paralaminar and not intralaminar sites.

Autoradiography provides a sensitive marker for terminations of CIN/Po projections in layer I. Amino acids injected into this nucleus in the opossum label projections that terminate nearly exclusively in layer I of somatosensory-motor cortex (Donoghue and Ebner, 1981). Interestingly, although the areal extent of these projections is identical to that of Po in the rat (Fig. 9), the pure layer I termination pattern resembles that of VM in the rat and not Po. This species difference will be discussed later (Section 6.2.3).

In the bushbaby, a primitive primate, Po has been shown to project to primary somatosensory cortex (Pearson and Haines, 1980). Diamond (1982) has recently used the term CIN in the bushbaby to denote a medial portion of the Po complex situated laterally adjacent to the centre median (CM) nucleus of the intralaminar complex. He illustrates widespread CIN/Po as well as CM projections distributed throughout motor and somatosensory cortical areas. Further work is needed to determine if these nuclei project to superficial and deep layers, respectively, throughout this wide extent.

4.1.2. Projections to Layer I of Visual Cortex

Benevento and Ebner (1971) appear to have been the first to demonstrate extrageniculate projections to area 17. Large thalamic lesions sparing the lateral geniculate nucleus produced terminal degeneration in layers I, V, and VI of the

opossum striate and peristriate areas. Layer I projections in the rat have been found in the visual areas after amino acid injections of Re (Herkenham, 1978a), VLpl (Figs. 6, 7), VM (Herkenham, 1979), AM (Rieck and Carey, 1982c), and LP (Fig. 8 and Herkenham, 1980a). Thus, two general thalamic regions contribute projections to layer I—one anterior (Re, AM, VLpl, and VM) and the other posterior (LP). Large lesions of the anterior thalamus produce layer I degeneration in visual cortex of the hedgehog (Gould *et al.*, 1978). This degeneration was assumed to originate in an anterior intralaminar nucleus (AIN), but the more likely origins are the rostral paralamina nuclei which appear to be involved in the large lesion.

In the tree shrew and bushbaby, labeling of anterior thalamic structures occurs after HRP is confined to the superficial layers of striate cortex (Carey *et al.*, 1979). In both species labeling of rostral intralaminar neurons is charted, but in the bushbaby large numbers of cells are charted also in VA (Carey *et al.*, 1979). Rieck and Carey (1982a) have analyzed the rostral thalamic labeling in relation to the intralaminar nuclei, which they located on the basis of intense acetylcholinesterase (AChE) staining. According to their report, the rat and tree shrew show comparable patterns of labeling after superficial or deep HRP injections in visual cortex: in both species HRP applied to layer I labels cells in AChE-poor regions consisting of the AM, VA, and VM nuclei next to the internal medullary lamina, whereas HRP injected into infragranular layers labels central lateral (CL) and paracentral (Pc) cells embedded in the AChE-rich internal medullary lamina.

The posterior thalamic sites of origin of layer I projections to visual cortex include LP in the rabbit (Townes *et al.*, 1982) and hedgehog (Gould *et al.*, 1978). As in the rat, LP in these species projects to both areas 17 and 18 and shows area-dependent lamination in the deeper layers. In the bushbaby and tree shrew, the pulvinar nucleus is the origin of the layer I projections (Carey *et al.*, 1979).

4.2. Cats

Data on the domestic cat have been important in the historical development of ideas of thalamocortical connectivity; virtually all of the early electrophysiology was performed in this animal, and the concept of a nonspecific thalamus was developed from this work. Although the thalamus and cortex of the cat differ from those of the rat, homologies can be established, and it appears that the basic tripartite scheme outlined for the rat obtains in the cat as well.

As in the rat, the intralaminar nuclei of the cat thalamus are rather distinct in cytoarchitecture and project in a complex topographic pattern to most of the neocortex (Jones and Leavitt, 1974; Itoh and Mizuno, 1977; Kennedy and Balcydier, 1977; Macchi *et al.*, 1977, 1984; Hendry *et al.*, 1979; Cavada and Reinoso-Suárez, 1983; Macchi and Bentivoglio, this volume). Current investigations include attempts to better define the topography and areal range of individual intralaminar axons in cortex (Bentivoglio *et al.*, 1981). In addition, intralaminar projections to striatum are being examined in relation to intralaminar-cortical projections; recent data indicate that very few cells project to both striatal and cortical targets (Steriade and Glenn, 1982; Macchi *et al.*, 1984). Cells that project

to striatum are not completely intermingled with those which project to cortex, but instead are mostly confined to the innermost tier of cells within the internal medullary lamina (Sato *et al.*, 1979; Macchi *et al.*, 1984).

These observations suggest that the existence of a striatal projection should not be a major criterion for inclusion within the intralaminar system. Criteria for distinguishing intralaminar from paralamina nuclei should include features of cell size and shape, and location with respect to fiber and AChE staining. In addition, the present scheme adds the laminar target of cortical projections as a critical distinguishing feature which could be most directly examined by comparing the locations of retrogradely labeled cells after superficial and deep HRP injections in various cortical areas. An alternative approach would involve confining anterograde tracers to discrete thalamic nuclei and comparing laminar termination patterns. Neither of these approaches has been used extensively in the cat. In one revealing study, Miller and Benevento (1979) deposited amino acids in CL and adjacent nuclei, labeling projections to layers I and VI of primary visual cortex. Further work is needed to establish whether different cells project to deep and superficial layers and if so, whether they are localized to intralaminar and paralamina zones, respectively.

In another important study, HRP was used as an anterograde marker; when it was deposited into VM of the cat, it labeled cortical projections distributed exclusively in layer I (Glenn *et al.*, 1982). The areal extent of VM projections in the cat is reported to be much more limited than in the rat, covering only motor areas rostral to the cruciate sulcus (Glenn *et al.*, 1982). However, retrograde cell labeling in VM after cortical HRP injections in and around the anterior ectosylvian sulcus (Roda and Reinoso-Suárez, 1983) indicates a larger field of distribution.

Retrograde transport data suggest multiple cortical targets of projections arising from paralamina VA–VL in the cat. Like the projections of VLpl in the rat, the projections of cat paralamina VA extend from the frontal pole (Vedovato, 1978) to at least as far caudally as visual association cortex (area 20) (Cavada and Reinoso-Suárez, 1983). Such projections may terminate at least in part in layer I; the existence of a cerebello-thalamo-parietal cortical pathway leading through VL and terminating in superficial layers of cortex was proposed some time ago by Sasaki and co-workers (Sasaki *et al.*, 1970, 1972, 1975) on the basis of responses evoked by electrical stimulation of the cerebellum or thalamus. Anatomical studies confirmed this connection and demonstrated that the source of the parietal projection is the paralamina part of VL (Mizuno *et al.*, 1975; Tanji *et al.*, 1978; Hendry *et al.*, 1979).

Amino acids placed in paralamina VL label projections with area-dependent lamination; VL fibers terminate primarily in layer III of the frontal motor area but also in layers I and IV of parietal areas 5 and 7 (Hendry *et al.*, 1979). Henry *et al.* (1979) argued that the parietal connection is not a nonspecific one, since the dominant layer of termination is layer IV. However, other nuclei in the posterior thalamus appear to be the main relays to layer IV of these parietal areas (Graybiel, 1972; Mizuno *et al.*, 1975; Robertson, 1977; Tanji *et al.*, 1978). Significantly, HRP deposited in superficial layers of areas 5 and 7 labels cells only in the paralamina VA–VL, but HRP placed in the middle and deep layers of the same cortex labels cells located mainly in the LP–pulvinar complex (Oka

et al., 1982). It appears that this part of cat cortex, like most areas of rat cortex, receives multiple convergent thalamic inputs which are not confluent, but rather segregated by their different lamination patterns. The middle suprasylvian gyrus, where areas 5 and 7 are located, is a prime location for recording recruiting responses (Morison and Dempsey, 1942). Hence, it has been argued that the projection of paralamina VA–VL to these areas is the anatomical substrate relaying recruiting responses to parietal cortex (Sasaki *et al.*, 1970; Glenn *et al.*, 1982; Oka *et al.*, 1982).

If the organization of the posterior thalamus of the cat is similar to that of the rat, then the predicted origins of the layer I system are Po, LP, and MGm. Early degeneration studies in the cat suggested that the lateral and medial subdivisions of Po respectively project to layer IV in auditory and somatosensory cortical fields (Heath and Jones, 1971; Graybiel, 1973). Unfortunately, these studies have not been repeated with anterograde transport techniques. The results of retrograde HRP transport indicate that the medial portion of the Po complex has widespread connections which span several somatosensory fields, including the first, second, and third somatosensory areas (Tanji *et al.*, 1978; Spreafico *et al.*, 1981; Bentivoglio *et al.*, 1983).

The projections of the LP complex cover widespread cortical territories in the cat. Amino acids placed in the lateral portion, LP1, label projections to layer I of visual areas 17, 18, 19, 20, 21 and the Clare–Bishop area (Miller *et al.*, 1980; Symonds *et al.*, 1981). As in the rat, area-dependent lamination characterizes projections to deeper layers; terminations are found in layer IVc/V in area 17 and in layers III and IV/V in areas 18, 19 and the Clare–Bishop area (Miller *et al.*, 1980).

Anterograde transport data describing MGm projections in the cat are lacking. However, the results of retrograde HRP transport show that MGm projects to virtually all subdivisions of auditory cortex in the cat (Raczkowski *et al.*, 1975; Winer *et al.*, 1977; Andersen *et al.*, 1980). Results obtained by the anterograde degeneration method suggest that MGm contributes more fibers to layer I than does the principal part of the MG complex (Niimi and Naito, 1974).

4.2.1. The Recruiting Response

The anatomical basis for the recruiting response has been analyzed in investigations (Sasaki *et al.*, 1970, 1975; Sasaki, 1975; Herkenham, 1979; Glenn *et al.*, 1982) in which data from axonal transport studies have been correlated with findings based on physiological techniques. One major consensus is that the “final paths” for the transmission of recruiting to cortex lie in paralamina nuclei, notably VM and paralamina VA–VL in the cat (Sasaki *et al.*, 1970, 1975; Sasaki, 1975; Glenn *et al.*, 1982).

Several factors have contributed to this narrowing of candidates. One is the apparent discovery that recruiting responses do not occur in nearly all of the cortex as was claimed by one group (Jasper, 1961). When bipolar concentric electrodes (Starzl and Magoun, 1951) or microelectrodes (Sasaki, 1975) are used so that only local events are recorded, recruiting responses appear restricted to regions anterior to the cruciate sulcus, the cingulate cortex, rostral portions of the middle suprasylvian gyrus, and, perhaps, a portion of the posterior supra-

sylvian gyrus. None of these sites is in primary sensory cortical areas. Many factors other than recording techniques determine whether a given cortical area will manifest recruiting potentials (e.g., level of anesthesia). Even so, rostral frontal and middle suprasylvian cortices have always been considered recruiting centers (Morison and Dempsey, 1942).

Nuclei in which low-frequency electrical stimulation can elicit cortical recruiting are marked in Fig. 1. The nonspecific thalamus, defined on the basis of this phenomenon, includes intralaminar, paralaminar, and reticular nuclei. Though all nonspecific nuclei were found to be capable of generating recruiting, they differed with respect to various factors, such as: cortical sites of elicited response, latency to onset of recruiting, depth of anesthesia required to permit recruiting, and so on (Jasper, 1954, 1961). Recruiting was best obtained by stimulating the anterior VM and adjacent VA (Starzl and Magoun, 1951; Hanbery and Jasper, 1953; Hanbery *et al.*, 1954). Laminar analysis of recruiting suggested that the response was generated by synaptic events occurring initially in layer I (Li *et al.*, 1956; Spencer and Brookhart, 1961; Foster, 1980).

Glenn *et al.* (1982) provided anatomical evidence that a distinct set of thalamocortical fibers could be the substrate for the initial recruiting potential in layer I. They used anterograde HRP transport to show that VM projects to layer I in the cat, though to a limited expanse of cortex. They also showed that selective depolarization of the superficial layer of the target area, precruciate cortex, by Mn^{2+} superfusion selectively suppressed the VM-evoked wave. These results support and extend an earlier proposal (Herkenham, 1979) that VM is the final efferent path mediating recruiting responses, and that other thalamic nuclei are capable of generating recruiting because of polysynaptic feedback connections, via cortex and/or the reticular nucleus, leading to VM.

It has already been noted that the nonspecific thalamus, defined as those nuclei that produce recruiting when stimulated, contains nuclei which either have no cortical projections or which project primarily to either deep or superficial layers. The implicit dogma for many years has been that the nonspecific thalamus is the origin of layer I projections, but this is not completely true. Not only does the physiologically defined nonspecific thalamus include nuclei that do not have such projections, but it also excludes some nuclei that do, such as the MGm. As will be argued in the next section, a different unifying system brings these nuclei into one functional category, not the nature of their cortical projections.

In this light, we can better question the need to "fit" the intralaminar nuclei into the layer I system. A few physiological studies have addressed the issue of lamination and have suggested that intralaminar stimulation can monosynaptically excite cortical projection neurons via contacts near the cell somata, in the deep layers (Araki and Endo, 1976; Endo *et al.*, 1977). During recruiting elicited by repetitive low-frequency intralaminar stimulation, microelectrode recordings at different depths of cortex show that the first responses to occur after each shock may occur simultaneously in superficial and deep layers, or often earlier in the deep layers (Li *et al.*, 1956; Spencer and Brookhart, 1961; Foster, 1980). Thus, intralaminar inputs to the deep layers may play an important role in generating recruiting.

The dominant and distinguishing feature of the recruiting responses is a

superficial negative wave that switches to a positive wave throughout the deeper layers. Variations on this pattern, the timing of the events leading to it, and the irregular association of cortical unit activity with the recruiting wave “emphasize the complexity of the recruiting response and the fallaciousness of over-simplified explanations for these potentials” (Spencer and Brookhart, 1961, p. 46). Indeed, some unit activity in layer IV-projecting nuclei is phase locked with recruiting and, therefore, must contribute to the phenomenon (Avoli, 1983).

4.2.2. The Reticular Nucleus

Nuclei that produce recruiting also become recruited when other nonspecific thalamic sites are stimulated (Starzl and Magoun, 1951), suggesting a system of selective interconnections among the affected structures. The role of the reticular nucleus in the integration and synchronization of nonspecific thalamic activity has been appreciated only recently. It had long been felt that the reticular nucleus might contain the “final neurons” for transmission of recruiting responses to cortex (Hanbery *et al.*, 1954). Intrathalamic connections, supposedly extensive among the nonspecific nuclei (Scheibel and Scheibel, 1967), were thought to transmit neural activity to other parts of the nonspecific thalamus and to the reticular nucleus. One group (Starzl and Magoun, 1951; Starzl and Whitlock, 1952) minimized the contribution of the reticular nucleus and included only its rostral pole in the recruiting system, while another adamantly included the entire nucleus though admitting the greater involvement of the rostral part (Jasper, 1954, 1961).

Subsequent anatomical data show that the reticular nucleus does not project to cortex at all, but instead projects back onto the thalamus; physiological data show that it provides a powerful inhibitory feedback on thalamocortical neurons (Scheibel and Scheibel, 1966, 1972; Schlag and Waszak, 1970; Jones, 1975b). The nature of this feedback inhibition makes it an ideal pacemaker for the rhythmic, low-frequency activity characteristic of the recruiting phenomenon. One important organizational feature of the feedback is topographical reciprocity; individual points in the thalamus are reciprocally connected with points in the reticular nucleus (Scheibel and Scheibel, 1966; Jones, 1975b). However, considerable convergence and divergence of connections (required for recruitment of other thalamic nuclei) is assured by the far-reaching extent of reticular nucleus dendrites (Scheibel and Scheibel, 1966).

Another important feature, as a mechanism for generating recruiting, is that the rostral pole of the reticular nucleus receives convergent inputs primarily from the nonspecific nuclei (Jones, 1975b; Nguyen-Legros *et al.*, 1982) and in turn projects mainly to the intralaminar and ventromedial nuclei (Fig. 12). The contralateral projection via the internal medullary lamina (Fig. 12) is also significant because recruiting responses are evoked bilaterally, though all dorsal thalamic projections are ipsilateral. Since other internuclear and crossed thalamic connections claimed from Golgi material (Scheibel and Scheibel, 1967) have not been identified with axonal transport techniques (Jones, 1981), the rostral pole of the reticular nucleus may play a key role in the selective transmission of impulses to the final paths in the intralaminar and VM nuclei. Perhaps only those nuclei with afferent access to the rostral pole of the reticular nucleus can

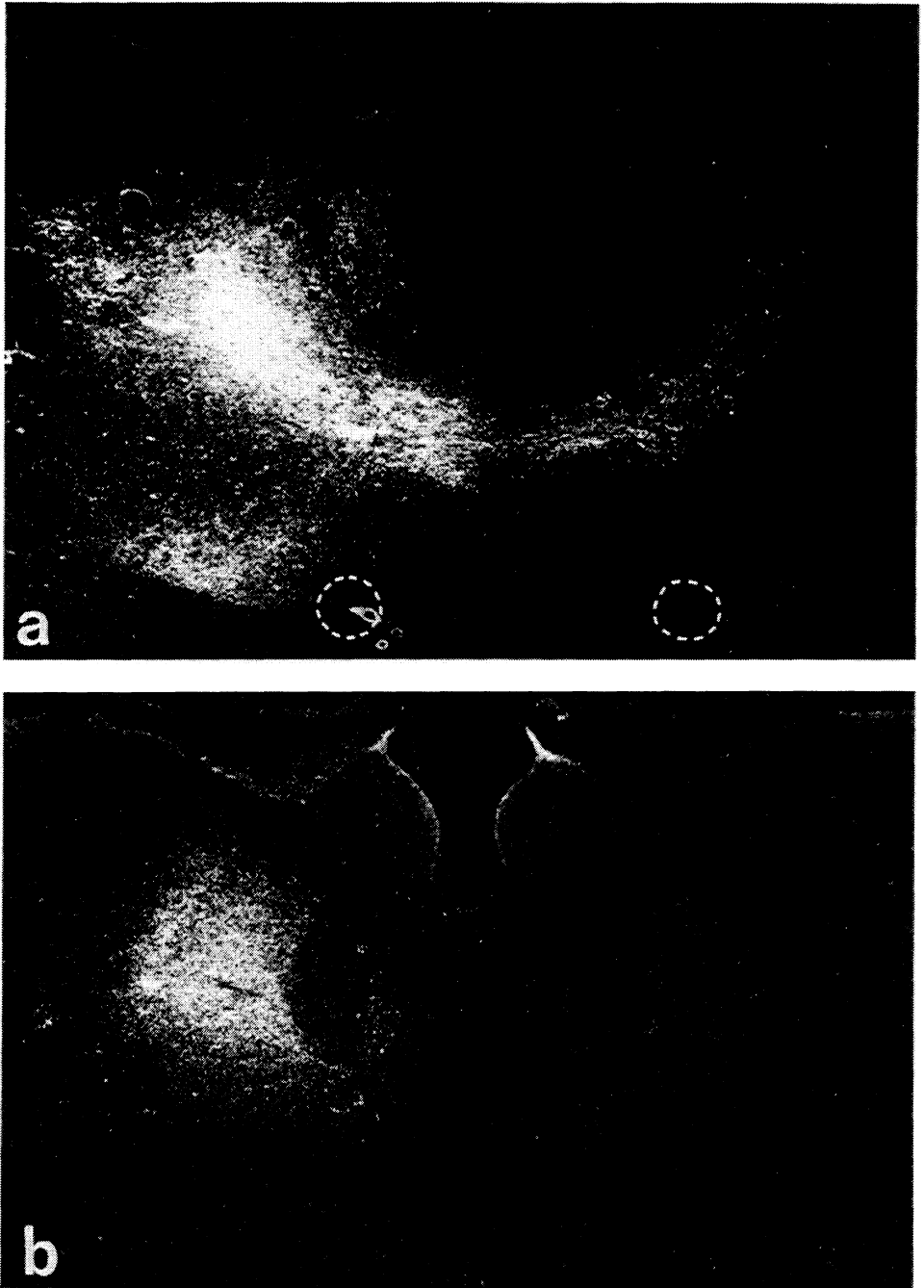


Figure 12. Darkfield photographs of two levels of rat brain, showing the distributions of projections of the thalamic reticular nucleus in a case in which the ventral part of the rostral pole region was injected (as at level of Fig. 3c). The mammillothalamic tract is outlined in (a) for orientation. Projections are distributed predominantly to the intralaminar and ventromedial nuclei (a) and to the parafascicular nucleus (b). Note the contralateral projection passing in the internal medullary lamina.

participate in recruiting during low-frequency stimulation of a given site. If so, then it is likely that nuclei with these connections constitute the functionally unified, physiologically defined nonspecific thalamus.

4.3. Monkeys

The existence of a nonspecific thalamocortical system in the primate with an organization similar to that of the cat would be expected on the basis of the similarities of the recruiting system in both species (see Starzl and Magoun, 1951; Starzl and Whitlock, 1952). Unfortunately, there have been no systematic attempts to reveal this system by placing anterograde tracers into the intralaminar and paralamina nuclei or by applying HRP to the superficial layers of cortex. Moreover, outside the intralaminar system it is difficult to know where to look for nuclei of origin (see Jones, 1975a). Structures in the monkey which appear to be homologous with VA-VL or Po in the rat, for example, are subdivided into many separate nuclei on the basis of distinct cytoarchitecture and connectivity (Jones, 1981). Large portions of such territories in the monkey appear to be specific because they project to intermediate layers of restricted cortical areas of cortex. By analogy with the rat, a likely source of nonspecific layer I projections is the territory which is immediately adjacent to the intralaminar nuclei.

Of the possible subdivisions of the ventral group, the only one that projects to the whole of the agranular motor area appears to be VLm (Schell and Strick, 1984). This is significant because VLm appears to be the homologue in the monkey to VM in the rat and cat; in all three species this nucleus receives input from the substantia nigra (Carpenter *et al.*, 1976). There are no data showing the areal extent or laminar distributions of the projections of VLm. Further work is needed, but it seems possible that some parts of the ventral complex are specific relays to discrete subdivisions of sensory-motor cortex, while others may have widespread nonspecific projections, possibly to layer I.

The VAmc nucleus, like VLm, lies adjacent to the intralaminar nuclei and receives nigral inputs (Carpenter *et al.*, 1976). The laminar distributions of VAmc projections are unknown, but there is no doubt that this paralamina nucleus innervates large parts of the frontal and parietal lobe. Cells in VAmc are labeled after HRP is injected into area 7 of the inferior parietal lobe (Divac *et al.*, 1977; Kasdon and Jacobson, 1978) and many areas rostral to the precentral gyrus (Kievit and Kuypers, 1977) in the rhesus monkey. In the chimpanzee, VAmc projects to visual cortex (Tigges *et al.*, 1983). This wide distribution resembles that of VLpl in the rat.

It seems that no portion of the Po complex projects to primary somatosensory cortex in the monkey (Jones *et al.*, 1979). Instead, Po appears to have specific layer III/IV projections to nonprimary sensory cortex; an autoradiographic study of the projections of the posterior thalamic nuclei disclosed only layer IV terminations topographically distributed in discrete subdivisions in the insular, parietal, and temporal cortex (Burton and Jones, 1976). However, recent HRP data suggest that the projections of medial Po (Pom) may be more widespread than originally described (Friedman *et al.*, 1983). Sparse, diffuse projections may

have been missed in the earlier autoradiographic study, in which only 2-week exposure times were used (Burton and Jones, 1976).

Data showing layer I projections to auditory and visual areas in the monkey are more pertinent to the issues at hand, as the projecting nuclei have been targets for amino acid injections, often after identification of their position by the results of cortical HRP injections. Jones and Burton (1976) illustrate fibers terminating in layer I of auditory cortex after amino acids were deposited in a region that included the MGm. The termination pattern closely matches that seen in the rat (Fig. 11).

In the visual system of the monkey the pulvinar complex has widespread topographic connections that cover striate and peristriate visual areas (Benevento and Rezak, 1976). A portion of the pulvinar (inferior and adjacent lateral) projects in area-dependent lamination fashion to layers I, II, and perhaps III of area 17 and to layers I and IV of area 18 (Ogren and Hendrickson, 1977; Rezak and Benevento, 1979). The laminar shift in termination occurs at the 17/18 border, whereas the density of termination in layer I does not change (Benevento *et al.*, 1975). These features resemble those of LP projections in the rat (Fig. 8).

Other thalamic nuclei that may have widespread connections in the monkey, based on retrograde HRP transport data, include VLc, which projects to both frontal (Schell and Strick, 1984) and medial parietal areas (Murray and Coulter, 1981); the medial pulvinar, which projects to frontal (Kievit and Kuypers, 1977), insular (Friedman *et al.*, 1983), parietal (Pearson *et al.*, 1978), and temporal areas (Burton and Jones, 1976); and reuniens, which projects at least to medial parietal (Murray and Coulter, 1981) and insular areas (Friedman *et al.*, 1983). Many of these nuclei are paralaminar and would be likely candidates for the origin of layer I projections. The last set of observations, from HRP experiments, is interesting since a large medial thalamic deposit of amino acids involving Re in the rhesus monkey labels a widespread cortical projection which, in frontal, insular, temporal, juxtallocortical, and hippocampal areas, terminates in layer I (Friedman, personal communication).

5. Cellular Origins of Layer I Projections

Anterograde tracing studies show that nearly all thalamic nuclei project to multiple laminar targets (e.g., Frost and Caviness, 1980). Moreover, they may all project to layer I, though it is important to note that only those in the layer I class have dense projections there. Multiple patterns of lamination could result either from the collateralization of axons into different layers or from the separate distributions of axons into single layers.

In primary visual cortex of cats and monkeys, studies in which cortical afferent fibers were physiologically characterized and then filled with HRP show that thalamic axons which arborize in intermediate layers form a class different from the class of axons which arborize in layer I (Ferster and LeVay, 1978; Blasdel and Lund, 1983). In the rhesus monkey, a parvocellular lateral geniculate neuron was identified on functional grounds as the source of an HRP-filled axon that arborized extensively in layer I and to a lesser degree in layer VI (Blasdel

and Lund, 1983). HRP confined to layer I of primary visual cortex labels small cells in the dorsal lateral geniculate (LGd) nucleus; these are confined to the medial interlaminar nucleus and the parvocellular C lamina in the cat (Leventhal, 1979) and to the interlaminar and parvocellular zones of the tree shrew and bushbaby (Carey *et al.*, 1979). LGd projections to layer I of squirrel monkey area 17 appear to arise almost exclusively from cells in the interlaminar zones (Fitzpatrick *et al.*, 1983; Weber *et al.*, 1983). Finally, HRP studies in the cat primary somatosensory (SI) cortex show that large cells in VP project to the intermediate layers while small cells scattered throughout this specific nucleus project to layer I (Penny *et al.*, 1982).

Cells with different laminar targets in cortex seem to intermingle in the VL complex. In the cat, electron microscopic data indicate that a high percentage (18%) of VL terminations in motor cortex are in layer I (Strick and Sterling, 1974). Yet a study by the technique of intraaxonal HRP filling of VL axons relaying cerebellar inputs to motor cortex showed that arborizations are confined to layers III and the upper part of VI (Deschênes and Hammond, 1980). These authors point out that there may be a sampling bias toward the penetration of larger axons; alternatively, layer I inputs may have a distinct site of origin in VL, perhaps outside the cerebellar-recipient zone. HRP data support differential localization of the layer I cells: injections in layer I of cat motor cortex label cells in the medial, paralaminar part of VL, while injections in deep layers label cells in the ventrolateral part (Oka *et al.*, 1982).

In the monkey motor cortex, electron microscopic data show VL terminations in layer I (Sloper, 1973), yet autoradiographic tracing of projections to MI from lateral parts of VPLo, the cerebellar-recipient zone in the VL complex, shows nearly exclusive termination in layer III (Friedman and Jones, 1981). Since autoradiography is not subject to sampling bias, it is reasonable to conclude that layer I projections originate in other parts of the VL complex. Cells in VPLo, VLc, and VLm are labeled after HRP injections in MI and in other parts of the motor field (Schell and Strick, 1984); perhaps these structures are the origins of widespread layer I projections in the monkey. Miyata and Sasaki (1983) combined HRP data with prior electrophysiological findings in the monkey to argue that superficial and deep projections from the VL complex arise from a complex arrangement of intermingled cell clusters.

Thus, it appears that layer I projections can arise from cells anywhere in the thalamus. Such cells can be randomly mixed with cells projecting to other layers, or they can be located in laminae, clusters, or more general districts within a thalamic nucleus. In the case of VM, they may be the only cell type within the nucleus. The categorization of nuclei according to their laminar mode of termination, therefore, is not rigid. As stated, the present categories in the tripartite model of thalamocortical organization are based on relative numbers of axons in the superficial, intermediate, or deep layers.

An understanding of the functional significance of the various arrangements of thalamic cells with layer I projections will ultimately require a thorough knowledge of the afferent connections that make synaptic contacts on them. Two features of afferentation are immediately relevant. One is the striking difference between the specific and nonspecific nuclei in terms of the nature and diversity of afferent sources, and the other is the manner in which afferent inputs

select their postsynaptic targets within a nucleus. The elaboration of these features is beyond the scope of this chapter, so the topics will be reviewed only briefly.

The anatomically defined nonspecific thalamus can be distinguished from the specific thalamus on the basis of convergent inputs from diverse locations. The intralaminar nuclei receive inputs from more than a dozen sources in the spinal cord, brain stem, cerebellum, basal ganglia, and cerebral cortex (see review by Macchi and Bentivoglio, this volume). The layer I-projecting nuclei also have multiple inputs, though fewer than the intralaminar nuclei and typically just a few of these are major afferent sources. VM, for example, receives a major input from the substantia nigra (Herkenham, 1979) but also a sparse input from the brain stem reticular formation (Herkenham, 1979; Robertson and Feiner, 1982). The specific nuclei only have one major ascending input system which largely defines their function. The term "nonspecific" thus acquires a new meaning; other workers have emphasized that the nonspecific nuclei must assimilate and integrate multiple afferent inputs (see Section 7).

Given these facts, it seems apparent that LGd neurons projecting to layer I carry a different kind of information than do the nonspecific nuclei. Also, the areal extent covered by the composite projection of the geniculate axons would be less than that covered by the composite projection of a given nonspecific nucleus.

These major distinctions must be modified by the implications of the second feature of afferentation, which is that layer I cells may be selectively targeted by, or excluded from, certain afferent inputs, regardless of their locations. The case of the LGd is well worked out. The restriction of layer I-projecting cells to the interlaminar zones results in the exclusion of inputs from the retina and the reception of inputs from the superficial layers of the superior colliculus (see Leventhal, 1979, and Weber *et al.*, 1983, for discussion). These cells may be located within the boundaries of LGd, but they do not receive the retinal input as does the rest of the nucleus.

Similar data are not available for other nuclei, but a recent observation is suggestive. In the MGm, Winer and Morest (1983) used Golgi stains to distinguish among various types of afferent fibers. They show that different kinds of afferent networks can be found in selective association with either large or small cells. It is not known whether these cell types have differential laminar targets in cortex. Future work with double-label techniques to label throughput systems should be revealing.

6. Speculation on the Phylogeny of the Nonspecific Thalamus

Despite a relative paucity of data, the broad new framework proposed in this chapter can be examined from a phylogenetic perspective. This is useful because a consideration of diverse species may underscore general principles of thalamic organization, and evolutionary trends may be useful in locating nonspecific thalamic structures and understanding their functions.

6.1. The Intralaminar Nuclei

The intralaminar system is often considered to be the thalamic component of the reticular formation (Jasper, 1954). As a member of the "isodendritic core" (Ramón-Moliner and Nauta, 1966), it has been regarded as having evolved earlier in vertebrate history than the rest of the thalamus. Surprisingly then, Ebner (1976) could find no evidence for the existence of a system resembling the intralaminar nuclei in the red-eared turtle (*Pseudemys scripta*), a species with brain organization that may bear resemblance to that of many nonmammalian vertebrates, including, it is assumed, those ancestral to mammals. In fact, the intralaminar system has not been identified in any nonmammalian vertebrate and is not obvious in the cytoarchitecture of the thalamus of the spiny anteater (echidna), a monotreme that is thought to be representative of primitive mammals (Welker and Lende, 1980).

In placental mammals the intralaminar system appears to be a relatively conservative set of nuclei whose size is proportional to the striatum as well as the cortex. However, there is a suggestion that the relationship with the striatum may be the more important determinant of its size. In monkeys and humans both CM and its main striatal target, the putamen (Jones and Leavitt, 1974), are large and clearly demarcated (Ajmone-Marsan, 1965). Yet of all the intralaminar nuclei, CM has the sparsest cortical projection relative to its striatal projection (e.g., Jones and Leavitt, 1974; Macchi *et al.*, 1977, 1984). Thus, the impressive size of CM in the human and other primates may have no relationship to the large expanse of cortex that is our evolutionary heritage. Although available evidence is minimal, and firm conclusions will require data from other reptiles and primitive mammals, a tentative suggestion is that the intralaminar nuclei appeared recently in evolution and are conservative.

6.2. Layer I-Projecting Nuclei

In contrast to the conservativeness of the intralaminar system among mammals, the layer I-projecting system shows radical species differences, if one can accept the homologies that have been suggested. Furthermore, layer I projections are found in several nonmammalian vertebrates, suggesting that some form of thalamic projection to layer I represents the ancestral mammalian pattern.

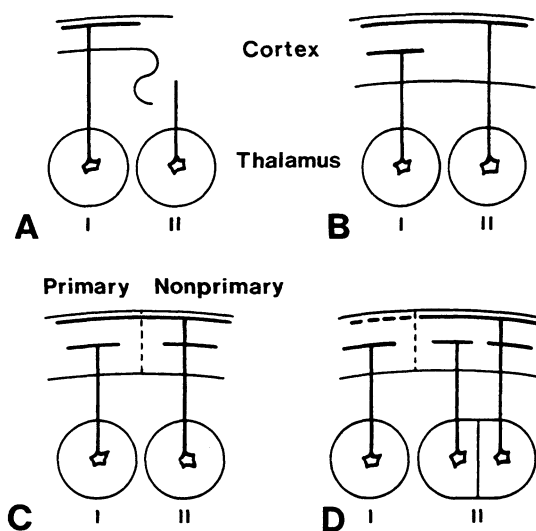
6.2.1. Nonmammalian Vertebrates

Sharks in their present form first appeared about 400 million years ago and seem to have had few selective pressures for structural modification since then (Ebbesson, 1980). Hence, thalamocortical organization in sharks may resemble that which existed in the ancestral land vertebrates, including mammals. Recent evidence shows that nurse sharks (*Ginglymostoma cirratum*) lack cortical lamination but otherwise have thalamotelencephalic circuits surprisingly similar to those of mammals (Ebbesson, 1980). Shark retinal fibers terminate in a diencephalic area named the lateral geniculate nucleus which, in turn, projects to the telencephalon

(Ebbesson 1972). Because of the lack of cortical lamination, specific and non-specific systems are not identifiable or differentiated in shark, but these observations make apparent the primordial arrangement of two parallel routes to visual cortex.

Turtles may resemble the reptilian predecessors of mammals (Hall and Ebner, 1970a,b). As represented schematically in Fig. 13A, two parallel visual systems can also be mapped in this primitive reptile. One is a retino-tecto-thalamo-telencephalic system; its last two stations are the nucleus rotundus, a diencephalic structure, and the dorsal ventricular ridge, a nonlaminated telencephalic structure. On connectional grounds, the nucleus rotundus appears to be the reptilian homologue of LP. Just lateral to it is another visual relay, the lateral geniculate nucleus, which receives direct retinal inputs and projects topographically to the laminated cortex (Hall and Ebner, 1970a,b). The geniculocortical connection, like all thalamocortical connections in the turtle, projects exclusively to the outer part of the molecular layer. Hence, the earliest-appearing thala-

Figure 13. Schematic plan of the connections of the specific and layer I-projecting nuclei at different stages of diencephalic and telencephalic evolution. The hypothesis provided in the text is that subdivisions or structures have been added to the cortex and thalamus in the course of evolution according to the sequence A to D shown here. Examples of the four patterns can be found in extant vertebrates. In all cases the left circle represents a specific sensory relay nucleus. The circle to its right in each case represents a nucleus of the paralaminal class, or its putative homologue. (A) The most primitive organization of thalamocortical circuits, suggested by the pattern of visual pathways in the turtle. The lateral geniculate nucleus (left) projects to layer I of general cortex, while the nucleus rotundus (right, the homologue



of LP in some mammals) projects to nonlaminated telencephalon. (B) A simple, perhaps primitive, thalamocortical organization in mammals. Cortex has six layers and the specific nucleus projects to an intermediate layer of a circumscribed cortical area. The paralaminal nucleus associated with the same sensory modality projects to layer I of the entire field. Examples are the projections of VP and Po in the opossum, and the principal MG and MGm in the rat. (C) The paralaminal nucleus has area-dependent lamination and projects to layer III and/or IV of a nonprimary cortical area as well as to layer I of the cortical field. Examples are Po and LP in the rat. (D) Portions of the paralaminal complex have only specific projections, and they are displaced laterally according to the hypothesized outside-to-inside gradient of thalamic evolution. The most medial site is still paralaminal, and it may project with area-dependent lamination to all or nearly all of the field. Examples may include the organization of the LP-pulvinar system in the cat and monkey. Variants on the pattern outlined in A–D include: layer I projections that extend beyond the confines of a modality-specific field, other patterns of area-dependent laminations, and the possible absence of a layer I projection from a paralaminal nuclear homologue. The intralaminar nuclei are not included in this scheme. Further details appear in the text.

mocortical fibers are the layer I type, and they arise from the connective homologue of the specific sensory relay nucleus.

6.2.2. Mammalian Cortex and Thalamus Elaborate Subdivisions

A major event in forebrain evolution may be the addition of structures that analyze features of sensory stimuli and generate appropriate nonreflexive responses. In the visual system the lateral geniculate nucleus is enlarged relative to the tectal relay nucleus. The cortex becomes six-layered and acquires a specialized mechanism for intrinsic information processing—the granular layer IV containing short-axoned, local-circuit stellate cells. Layer IV becomes the target for thalamocortical connections relaying direct sensory inputs from the periphery. The terminations of the lateral geniculate nucleus appear to be shifted from the distal to the more proximal shafts of pyramidal cell dendrites and to granule cells (Fig. 13B). Although there is no evidence, perhaps the rotundus/LP projection occupies the molecular layer vacated by geniculate terminals. Similar connective adjustments may occur in other modalities where parallel pathways can be found; extant examples include the organization of the auditory system in the rat and the somatosensory system in the opossum (Fig. 13B).

The major sensory modalities (vision, somatic sensation, audition) are separately represented in cortex, but they appear to have common organizational features and may have evolved along similar plans. Cortical areas unified functionally by the reception of sensory projections in a given modality have been termed cortical “fields” by Diamond (1979). In each field, elaboration of new cortical “subdivisions” occurs and is recognized by small changes in architecture. Overall, however, the cytoarchitecture within each field is similar, while differences between fields are major (Diamond, 1979), suggesting parallel evolution of the fields and their subdivisions. Thus, it is possible that when new cortical subdivisions appear during evolution, they can manifest various levels of cytoarchitectonic complexity; they may be more specialized (koniocortical) or primitive (allocortical or juxtallocortical), depending on the appearance of the cortex from which they are derived.

At the basis of this argument is the assumption that during the history of a cortical subdivision, it evolved a more complex structure. Structures that appeared earliest, such as primary visual cortex, might have specialized to the most complex forms. Visual areas, for example, show much more specialization of laminae than do auditory areas, possibly because audition appeared more recently in evolution (Sarnat and Netsky, 1974). Perhaps also, a recently added subdivision would tend to have a relatively primitive architecture, or at least appear somewhat more primitive than the subdivision it was derived from. This might explain why the “older” primary sensory areas have more complex structures than recently added nonprimary subdivisions of the same field.

It is proposed that thalamic nuclei evolve in a similar fashion and in parallel with cortical evolution. As cortical subdivisions are added, they are first innervated by the primitive form of thalamocortical projection, i.e., by nuclei that project to layer I of the new subdivision as well as to the rest of the field from which the subdivision is derived (Fig. 13B). Specialization of cortex and thalamus results in a shift of the thalamocortical projection from layer I to layer IV; in

the thalamus the nucleus of origin of the shifted projection may either lose its layer I projection or it may retain it by forming area-dependent lamination patterns, projecting to layer IV of the new subdivision and to layer I of the field (Fig. 13C). Most of the paralaminar nuclei in the thalamus of rats appear to belong in this category. In the visual system, for example, LP projects to layer IV of peristriate area 18 and to layer I of the entire visual cortex. In the somatosensory system, Po projects to layer IV of homotypical parietal cortex and to layer I of the primary and nonprimary somatosensory areas.

According to Diamond (1979) the unity of a field can be recognized by the demonstration of a single diffuse projection from one thalamic nucleus for each field. He provides evidence for projections of MGM and LP–pulvinar to all subdivisions of the auditory and visual fields, respectively. The data presented here extend this concept by showing that there are such nuclei for the three major sensory fields and one for what could be called the limbic field in the rat. Moreover, anterograde tracing data show that they project to layer I of the fields. Data illustrated in Figs. 5, 8, 9, and 10 show these points: LP projects to layer I of the visual field, MGM to layer I of the auditory field, Po to layer I of the somatosensory field, and Re to layer I of the limbic field.

Some nuclei in rats, like VM, VLp1, and the intralaminar nuclei, have widespread connections that extend beyond the confines of a single field. Diamond (1982) has recently suggested that such projections represent a general feature of thalamocortical organization among mammals.

6.2.3. Outside-to-Inside Direction of Thalamic Evolution

In the rat the nonspecific nuclei projecting to layer I of a sensory field are always situated just medial to the specific nuclei projecting to their targets in the same field. This feature suggests another general rule of thalamic organization. The rule is that the dorsal thalamus evolves from the outside in, just as in ontogeny the cells are born from the outside in (Rakic, 1977; Altman and Bayer, 1979). If the specific nuclei specialize out of nonspecific thalamic territory, then the specific nuclei lateral to their layer I-projecting nonspecific counterparts may have been displaced laterally by the proliferation of nonspecific cells medially. As new cortical subdivisions are created, so are thalamic afferent sources; these nuclei are inserted medially. They may subsequently become specific nuclei for the new cortical subdivision and migrate laterally, always leaving the more medial territory as the source of nonspecific layer I projections (Fig. 13D).

This medial/lateral arrangement is obvious in the major sensory systems. In the visual system the LGd is the first nucleus to innervate cortex, if the turtle represents the ancestral pattern (Fig. 13A). The mammalian LGd acquires layer IV projections largely confined to primary visual cortex. This can be viewed as a specialization within an established thalamocortical system. The more medial nucleus, LP, innervates layer I of the whole visual cortex in a nonspecific fashion (Fig. 13B), but in rats and other mammals examined it has specialized to also innervate layer IV of nonprimary visual cortex (Fig. 13C).

In the somatosensory system the homologue of VP in earliest vertebrate forms is a relay nucleus for the tactile sense (Ebbesson, 1980), and VP in mammals is the specific relay to layer IV of primary somatosensory cortex. Just medial

(inward) to it is Po, which in the generalized mammal, the opossum (*Didelphis virginiana*), projects exclusively to layer I of the whole somatomotor domain (Donoghue and Ebner, 1981). In rats Po projects additionally to layer IV of outlying regions of parietal cortex which, perhaps, are more recently added somatosensory subdivisions.

In the auditory system, the nonspecific layer I-projecting nucleus, MGm, is located medial to the principal relay portions of the medial geniculate complex. MGm does not project to layer IV of any part of the auditory field in rats, and may not in most mammals. Thus, the auditory pathways are best represented by the scheme in Fig. 13B. This "primitive" state may reflect the late arrival of audition in evolution (Sarnat and Netsky, 1974). Interestingly, auditory cortex in many mammals has "primitive" cytoarchitecture, notably a poorly developed layer IV.

In the motor system of the rat the specific and nonspecific portions of the VL complex are located respectively in lateral and medial parts of a cytoarchitecturally homogeneous nucleus. In other species separate nuclei within the complex are cytoarchitecturally and connectionally distinct. Present evidence suggests that some VL nuclei are specific and others nonspecific. According to the present scheme, specific connections would be expected to arise from lateral VL nuclei and the nonspecific connections from medial VL nuclei.

6.2.4. Primates

A very important question is, where are the nonspecific layer I nuclei in primates? The outside-to-inside hypothesis suggests that they will have paralaminar locations. There are very few anatomical data on the subject of widespread thalamocortical connections in the primate and even fewer on those which project to layer I. Electrophysiological studies of the cerebello-thalamo-cortical system in rhesus monkeys have shown that portions of the VA-VL complex can be stimulated to produce responses recorded by microelectrodes in upper cortical layers; these responses are similar to those associated with recruiting responses (Sasaki *et al.*, 1976a, 1979). The superficial cerebello-thalamo-cortical responses have been recorded in the hand and face areas of MI and in the premotor area. Interestingly, recruiting responses in the monkey frontal cortex had earlier been confined to areas rostral to the primary motor area (Starzl and Whitlock, 1952). Locating the thalamic sources of these superficial projections in monkeys has proven difficult. Perhaps cells or clusters of cells projecting to layer I are intermingled with clusters projecting to deep cortical layers of the frontal motor and "association" cortex (Miyata and Sasaki, 1983).

The areas of neocortex which are greatly expanded in primates and humans appear to be the frontal and temporal poles and the occipital lobe, with increases in relative volumes of adjacent parietal and insular cortex (Sarnat and Netsky, 1974). The expanded regions are the sites of the "association areas," which take up so much cortical territory in humans (Diamond and Hall, 1969; Diamond, 1979). These cortical areas in monkeys have not been shown to be "associational" in either the anatomical or psychological sense of the word, but rather they are nonprimary sensory/motor areas (Diamond, 1979). Nonprimary areas are the only areas that show recruiting responses in monkeys (Starzl and Whitlock, 1952).

In the rhesus monkey, recruiting loci, in addition to the intralaminar and reticular nuclei, are the mediodorsal and VA nuclei rostrally and the LP-pulvinar complex caudally (Starzl and Whitlock, 1952). These nuclei have projections to nonprimary cortex (Jones, 1981). Little is known about the lamination of their cortical projections, but it is noteworthy that at least some part of these nuclei would be expected to have projections to layer I as the anatomical substrate for the recruiting responses in primates.

The recruiting locations suggest projections to layer I of recently expanded "association" cortex in primates, supporting the general rule that newly added cortex is first innervated by layer I projections. The absence of recruiting in primary areas in monkeys raises the possibility that some areas may have lost layer I inputs from the thalamus as a consequence of specialization of the thalamic nuclei from the nonspecific layer I to the specific layer IV-projecting type (Fig. 13D). Perhaps in evolution the origin of the layer I projection can be shifted to the cortex, thereby forming the so-called "feedback" corticocortical connections from the nonprimary areas to layer I of the primary areas (Wong-Riley, 1978; Rockland and Pandya, 1979; Friedman, 1983).

7. Functional Considerations

The nonspecific thalamus has been considered as an important system for modulating cortical activity during sleep, arousal, selective attention, learning, and pain perception (Jasper, 1949, 1954, 1961; Krupp and Monnier, 1966). It is beyond the scope of this chapter to reevaluate the early work concerned with nonspecific thalamic function in light of the new understanding of the sources and targets of the deep and superficial projecting systems. Many of the early studies were carried out with little regard for the actual sites of thalamic stimulation, recording, or lesion; the histological data are often inadequate for reevaluation.

The system as a whole seems to be involved in maintaining or setting levels of cortical activity. The intralaminar nuclei are strategically positioned at the "cephalic" end of the reticular activating system (Jasper, 1954, 1958) and play a significant role in relaying reticular formation activity to cortex in states of wakefulness and sleep (Steriade, 1981; Glenn and Steriade, 1982). This is but one function of the nonspecific thalamus, however, and a comprehensive analysis must provide an understanding of how the same neurons that subserve this general function can also participate in very specific functions, such as controlling eye movements (Schlag and Schlag-Rey, 1971) and enhancing the perception of visual contrast (Hunsperger and Roman, 1976). The understanding will come from a thorough knowledge of the cortical areas and layers of termination of individual nuclei and the sources of afferent input to the nuclei.

An example of the consequence of a more thorough understanding of input-output relations of individual nonspecific nuclei is an appreciation that there are multiple forms of cortical activation, each under different afferent control. Three forms will be presented below.

7.1. Reticular Activation

Historically, the thalamic branch of the reticular activating system was found to be centered in the intralaminar system (Moruzzi and Magoun, 1949; Robertson *et al.*, 1973). Autoradiographic tracing studies show projections arising from the mesencephalic and pontine reticular formation which are dense to the intralaminar nuclei and sparse to the paralaminar layer I-projecting nuclei (Edwards and DeOlmos, 1976; Graybiel, 1977; Robertson and Feiner, 1982). Repetitive high-frequency stimulation of the mesencephalic reticular formation (MRF) causes an immediate and profound EEG desynchronization (Morison and Dempsey, 1942; Moruzzi and Magoun, 1949), which can also be recorded from animals during alert wakefulness and desynchronized sleep. The most likely connectional basis for the EEG changes is a direct intralaminar projection to deep layers, where axonal termination on proximal dendrites of pyramidal neurons could profoundly alter their threshold for excitation.

Studies of unit activity in CL during wakefulness and desynchronized sleep show that CL neurons fire tonically and more rapidly than during synchronized sleep, when they show bursts and pauses, often in phase with cortical spindles (Glenn and Steriade, 1982). In contrast, layer I-projecting cerebellar relay neurons in VA, which mediate recruiting in parietal cortex, show long latencies to respond to MRF stimulation and are initially suppressed by repetitive high-frequency stimulation (Sasaki, 1975; Sasaki *et al.*, 1976b). Thus, they appear to be indirectly connected with the MRF and, presumably, are inhibited by relayed activity in the reticular nucleus (Sasaki *et al.*, 1976b). Their role in tonic cortical activation seems to be indirect.

7.2. Motor Activation

There must be another form of cortical control exerted by the layer I-projecting nuclei mediating recruiting responses. Early studies based on stimulation and lesion methods had suggested that the pathways mediating cortical desynchronization were different from those mediating synchronization (Schlag and Chaillet, 1963; Weinberger *et al.*, 1965). Not surprisingly, the integrity of VA was required to maintain recruiting elicited by low-frequency intralaminar stimulation but not desynchronization elicited by high-frequency intralaminar stimulation (Weinberger *et al.*, 1965).

The recruiting nuclei, VA-VL and VM, may do more than shift into a bursting mode to induce cortical spindling in drowsy animals (Schmied *et al.*, 1979). Their specific role deserves further study. Attention should be focused on the sources of afferent control of these nuclei, notably the cerebellum, substantia nigra, and globus pallidus. These three sources are contained within circuits subserving motor control. The anatomy suggests that they have access to widespread layer I projections which could alter cortical activity in a subtle but universal way, by contacting the distal ends of apical dendrites of all of the pyramidal cells in the deeper layers. Thus, cortical output excitability in widespread areas is controlled by the cerebellum and basal ganglia. The control might

be manifested in the initiation and execution of programmed movements (Schmied *et al.*, 1979), and in locomotion and the control of posture (Starr and Summerhayes, 1983).

Perhaps the control is also manifested in the complex interaction between mood and movement. For example, immobility in animals produced by stressful situations has been termed "learned helplessness" or "behavioral despair" and has been likened to reactive depression in humans. The immobility can be reduced by activating the dopamine system (Willner, 1983), whose outputs lead from the striatum to the pallidus and substantia nigra and from these sites to the VA-VL and VM nuclei. Immobility, described as the arrest reaction or catalepsy, has also been generated in awake animals by nonspecific thalamic stimulation (Hunter and Jasper, 1949) and by application of the GABAergic agonist, muscimol, to VM (Starr and Summerhayes, 1983).

7.3. Sensory Activation

Just as the reticular formation and the extrapyramidal motor system have separate nonspecific thalamic systems with which to gain access to many areas of cortex, the major sensory channels may have a third and separate system as well. The third system comprises LP, Po, and MGm, which project to layer I of sensory fields. Neurons in these posterior thalamic nuclei are generally considered to be multimodal; microelectrode recording experiments show that they respond to peripheral stimulation in two or more of the visual, somesthetic, and auditory modalities (see review by Winer and Morest, 1983). The relayed transmission reaches widespread sensory cortical areas and, presumably, alters thresholds for cortical neuronal excitability via the superficial projections (e.g., Brown and Marco, 1967).

The consequences of this kind of cortical activation have not been examined under conditions which distinguish it from other kinds of nonspecific thalamic input, notably intralaminar. Though the early physiologists argued conceptually that phasic and regionally selective cortical activation could result from neuronal events in the intralaminar nuclei (Jasper, 1958), current thinking is that tonic cortical activation is mediated by the intralaminar nuclei (Steriade, 1981; Glenn and Steriade, 1982). Perhaps phasic, local activation subserving "selective attention" (Jasper, 1958) is mediated by the posterior layer I-projecting nuclei.

Alternatively, special features of a sensory modality may be processed by the posterior group of layer I-projecting nuclei. For example, pain is a sensation that is an obvious candidate for producing widespread cortical activation, yet responses to noxious stimulation have been recorded in all three divisions of the tripartite thalamus, namely the parafascicular nucleus (Pershanski *et al.*, 1981; Anderson and Dafny, 1983), Po (Poggio and Mountcastle, 1960), submedius (gelatinosus) (Craig and Burton, 1981), and VP nuclei (Honda *et al.*, 1983). It is possible that the specific and nonspecific thalamic nuclei convey information about different functional aspects of pain (affective, acute arousal, localization, and discriminative), though these aspects have only been tentatively assigned to each nucleus (Perl and Whitlock, 1961; Craig and Burton, 1981; Honda *et al.*,

1983). A better knowledge of the targets of the thalamocortical connections will greatly aid future work in which such functional issues are addressed.

Note added in proof. Since the completion of this chapter, several relevant works have been published. The concept of a "paralaminar" system in the thalamus is elaborated in Rieck and Carey (1985), and a relevant hypothesis of a "parcellation" process in neuronal ontogeny and evolution appears in Ebbesson (1984).

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