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COMMENTARY

VIEWPOINT: THE CORE AND MATRIX OF THALAMIC ORGANIZATION

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Abstract—The integration of the whole cerebral cortex and thalamus during forebrain activities that underlie different states of consciousness, requires pathways for the dispersion of thalamic activity across many cortical areas. Past theories have relied on the intralaminar nuclei as the sources of diffuse thalamocortical projections that could facilitate spread of activity across the cortex. A case is made for the presence of a matrix of superficially-projecting cells, not confined to the intralaminar nuclei but extending throughout the whole thalamus. These cells are distinguished by immunoreactivity for the calcium-binding protein, D28K calbindin, are found in all thalamic nuclei of primates and have increased numbers in some nuclei. They project to superficial layers of the cerebral cortex over relatively wide areas, unconstrained by architectonic boundaries. They generally receive subcortical inputs that lack the topographic order and physiological precision of the principal sensory pathways. Superimposed upon the matrix in certain nuclei only, is a core of cells distinguished by immunoreactivity for another calcium-binding protein, parvalbumin, These project in highly ordered fashion to middle layers of the cortex in an area-specific manner. They are innervated by subcortical inputs that are topographically precise and have readily identifiable physiological properties.

The parvalbumin cells form the basis for sensory and other inputs that are to be used as a basis for perception. The calbindin cells, especially when recruited by corticothalamic connections, can form a basis for the engagement of multiple cortical areas and thalamic nuclei that is essential for the binding of multiple aspects of sensory experience into a single framework of consciousness. © 1998 IBRO. Published by Elsevier Science Ltd.

Key words: thalamus, primates, cell-specific cortical projections, arousal, consciousness.

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1. INTRODUCTION

The thalamus and the cerebral cortex are inextricably linked, structurally and functionally. A massive array of thalamocortical connections serves to project the activities of thalamic neurons onto the cortex and alterations in the behaviour of large ensembles of thalamocortical relay cells, which are accompaniments of changes in the conscious state,

Abbreviations: CAMKII-α, alpha-type II calcium/calmodulin-dependent protein kinase; CL, central lateral nucleus; CO, cytochrome oxidase; LGd, dorsal lateral geniculate nucleus; Li-SG, limitans-suprageniculate nucleus; MGad, anterodorsal medial geniculate nucleus; MGmc, magnocellular medial geniculate nucleus; MGpd, posterodorsal medial geniculate nucleus; MGv, ventral medial geniculate nucleus; Pla, anterior pulvinar nucleus; Po, posterior nucleus; VLa, anterior ventral lateral nucleus; VLp, ventral lateral posterior nucleus; VMb, basal ventral medial nucleus; VPI, ventral posterior inferior nucleus; VPL, ventral posterior lateral nucleus; VPM, ventral posterior medial nucleus.

are reflected in the electroencephalographic waves recorded from the surface of the cortex and which serve as indices of levels of consciousness.[68,69]

Historically, a belief has grown up in the existence of two fundamentally different sets of thalamocortical connections, which play different roles in state-dependent activities of the forebrain. One, arising from neurons in the principal relay nuclei, is highly organized topographically and projects to middle layers of the cerebral cortex; in the case of the sensory relay nuclei it is closely linked to the peripheral sense organs and is considered for obvious reasons to form part of the pathway to perception; the other, arising from the intralaminar and perhaps associated nuclei, is diffusely organized, projects widely upon superficial layers of the cerebral cortex, is less closely linked to the periphery and is thought to be involved in some more generalized aspect of forebrain function.[19,31,32] The putative function of this diffusely projecting, superficial cortical projection was originally thought to be manifest in the recruiting response, a long-latency, high-voltage, slow, surface negative potential that spreads across the cerebral cortex, waxing and waning as it does so, following low frequency stimulation of the intralaminar nuclei.[19,32,51] The recruiting response was thought to depend upon the presence, close to the cortical surface, of the terminations of a unique set of thalamocortical fibres arising in the intralaminar nuclei.[44] In the years that have followed demonstration of the recruiting response, it has been shown that although the major outflow of the intralaminar nuclei is to the striatum, substantial numbers of their cells do, indeed, project to the cerebral cortex,[37,71] although not as diffusely as originally proposed.[45,46] However, the origin of the superficial cortical projection may not be confined to the intralaminar nuclei but extend to other adjacent nuclei such as the ventral medial[45,71] and its exact layer(s) of termination in the cortex remain controversial.[1,5,25,40,59,73]

In recent times, the idea of a diffuse thalamocortical projection that may serve, as the recruiting response was thought to do, to regulate the spontaneous electrical rhythms of the cerebral cortex that accompany changes in behavioural state, has largely fallen into disrepute. Instead, the trend is to view thalamic cells in all nuclei, apart from the intrinsic GABAergic interneurons, as physiologically essentially similar.[30] Although relay cells in the caudal part of the central lateral nucleus, (one of the intralaminar nuclei), in the cat are reported to be capable of unusually high rates of burst discharge in comparison with other relay cells[18] and possess a number of other distinguishing properties, such cells are quite rare, are not ubiquitously distributed, and have not been encountered in investigations on other species.[23] There is also a trend to see the various state-dependent thalamocortical rhythms as depending on the collective oscillation of large ensembles of thalamic relay neurons, independent of any differences in the extent or laminar terminations of their axons within the cortex.[9,12] Mechanisms and pathways are needed, however, for the spread of rhythmicity across thalamic nuclei and cortical areas, in order to engage the whole thalamus and cerebral cortex during changes in behavioural state.[10,43,68–70]

2. A NEW POINT OF VIEW

The present viewpoint, which has arisen from recent work on the chemical identities of thalamocortical relay neurons in monkeys, provides one basis for the recruitment of thalamic nuclei and cortical areas into collective action. It does so, by generalizing the idea of a diffuse, superficially-projecting and a focused middle layer-projecting thalamocortical system to the whole thalamus, unconstrained by the older, polarized view of their restriction to the intralaminar and principal nuclei, respectively.

The idea (Fig. 1) is that a set of superficially projecting thalamocortical neurons is distributed throughout the dorsal thalamus, unconstrained by nuclear borders or by differences between intralaminar and other nuclei, and forms a matrix to the whole thalamus. Upon this matrix, in certain nuclei, is imposed a core of middle layer-projecting thalamocortical neurons whose thalamic distribution is constrained by the classical nuclear borders, and which is particularly evident in the sensory and motor relay nuclei. Every nucleus, intralaminar and principal, contains the matrix cells but only some contain the core cells as well. Typically, where core cells are absent, there is an elaboration of the matrix, more matrix cells being present than in nuclei in which core cells and matrix cells are intermingled.

The idea is extended further in the light of evidence about input-output connections: the core cells and nuclei in which a core is present, receive subcortical inputs that are highly ordered topographically, and the axon terminations are confined within nuclear borders of the thalamus. In the case of the principal sensory relay nuclei the core cells and their inputs have well-defined receptive field properties and strong stimulus–response coupling, and the cells project with the same high degree of topographic order upon one or a few fields of the cerebral cortex, their terminations limited by the architectonic and functional boundaries between fields. By contrast, the matrix cells and nuclei in which the matrix is enhanced, receive more diffuse subcortical inputs whose distribution is not restricted by thalamic nuclear borders. These inputs and the cells upon which they terminate, although retaining some relationship to the periphery, commonly lack easily definable receptive fields and show less precise stimulus–response coupling. The recipient thalamic cells project diffusely to more than one area of the cerebral cortex, in this case unconstrained by architectonic or functional boundaries. The diffuse inputs are not to be confused with the non-specific

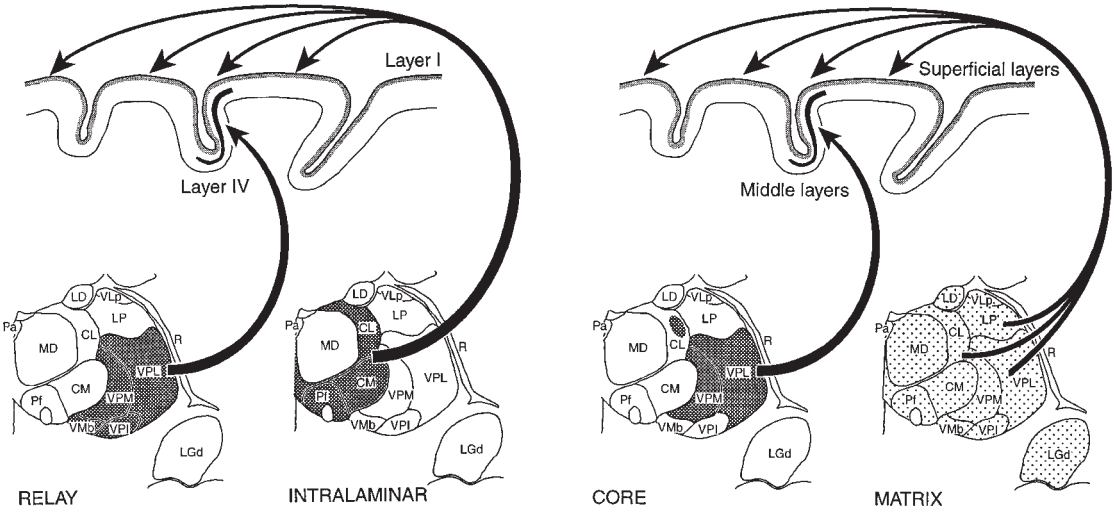

Fig. 1. (Left) The traditional view of thalamocortical connections. Relay nuclei such as the ventral posterior, are considered to project primarily to layer IV of the cerebral cortex, the projection constrained by the borders of a functional cortical area, such as the somatosensory area. The intralaminar nuclei, by contrast, are considered to project to layer I of the cortex over wide areas, unconstrained by the architectonic or functional borders between cortical areas. (Right) The new view proposed in the present account. Area-specific projections to middle layers of the cortex arise from a core of cells that are found in the sensory and certain other relay nuclei and in some of the intralaminar nuclei. Widespread superficial layer projections arise from a matrix of cells extending through the whole thalamus and unconstrained by borders between nuclei or by the division of the thalamus into intralaminar and principal nuclei. CL, central lateral nucleus; CM, centre median nucleus; LD, lateral dorsal nucleus; LGd, dorsal lateral geniculate nucleus; LP, lateral posterior nucleus; MD, mediodorsal nucleus; Pa, paraventricular nuclei; Pf, parafascicular nucleus; R, reticular nucleus; VLp, ventral lateral posterior nucleus; VMb, basal ventral medial nucleus; VPI, ventral posterior inferior nucleus; VPL, ventral posterior lateral nucleus; VPM, ventral posterior medial nucleus.

cholinergic and monoaminergic brainstem afferents to the thalamus, whose actions upon thalamic cells may represent one of the most powerful state-dependent drives to the thalamus.[68,69] In the present context, the diffuse input pathways are those such as the spinothalamic tract and those brainstem auditory pathways which ascend to the thalamus independently of the more direct route from the ventral cochlea nucleus via the inferior colliculus.

3. THE EVIDENCE: TWO CLASSES OF THALAMIC RELAY CELL

The evidence upon which this viewpoint is based is derived from studies of the distribution and connections of populations of thalamic cells identified in the monkey thalamus by immunoreactivity for the calcium binding proteins, parvalbumin and 28,000 mol. wt calbindin,[16,22,36,49,60–62] with some ancillary data drawn from immunostaining or *in situ* hybridization histochemistry for other neuron-specific proteins or mRNAs.[4,24,34,72] To present the case, examples will be drawn from three nuclei or nuclear complexes: the ventral posterior nucleus and its environs, the medial geniculate complex, and the dorsal lateral geniculate nucleus. Other nuclei, including those of the intralaminar group, will be referred to later. In all the examples, it will be shown that calbindin cells form a matrix extending through all nuclei, while parvalbumin cells are imposed only on certain nuclei or subnuclei. Where parvalbumin cells are absent, the calbindin cells show local increases in number.

3.1. Ventral posterior complex

The ventral posterior complex of nuclei is made up of the ventral posterior medial (VPM) and ventral posterior lateral (VPL) nuclei, which form the principal thalamic relay to primary somatosensory cortex, and a number of associated nuclei, notably the basal ventral medial nucleus (VMb) and the ventral posterior inferior nucleus (VPI), which form the visceral, taste and other ill-defined thalamic relay centers. Parvalbumin-immunoreactive cells predominate in VPM and VPL and are absent from VMb and VPI (Fig. 2). In VPM, the parvalbumin cells are confined to the ''rods'': anteroposteriorly elongated aggregations of relay cells, rich in cytochrome oxidase (CO), that form the morphological correlates of the thalamic representation of the face and of peri- and intra-oral structures.[61,62] In VPL, the parvalbumin cells tend to aggregate in lamella-like arrays, conforming to the representation pattern of the rest of the body surface.[60] Unlike parvalbumin cells, calbindin-immunoreactive cells are found throughout all four nuclei of the ventral posterior complex, overlapping the distributions of parvalbumin cells in

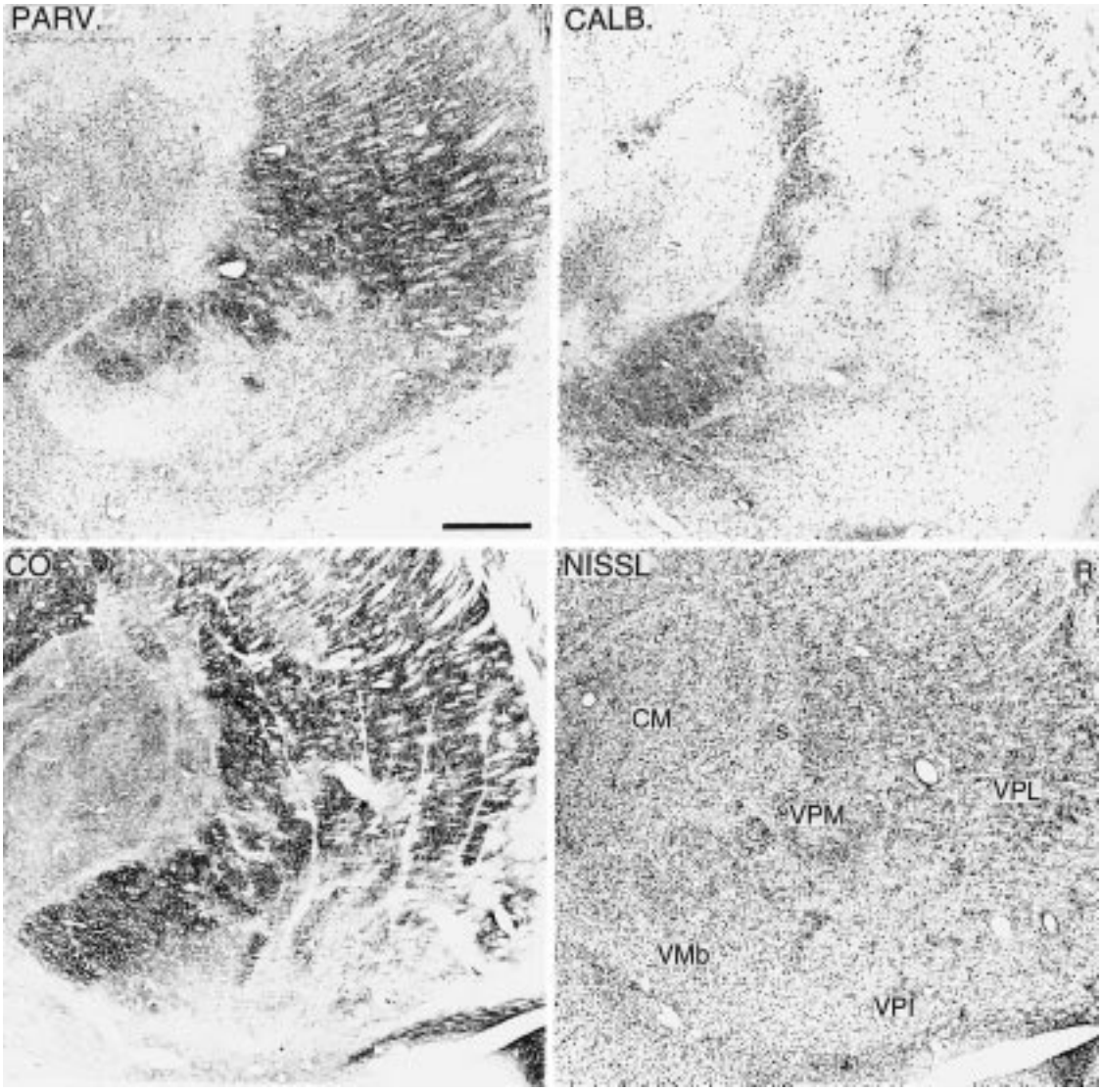

Fig. 2. Adjacent frontal sections through the same thalamus of a macaque monkey, stained immunocytochemically for parvalbumin (PARV.) or calbindin (CALB.), histochemically for cytochrome oxidase (CO) or with thionin (NISSL), showing the restriction of parvalbumin cells to the VPL and VPM nuclei and to regions rich in CO activity. Calbindin cells, by contrast, extend throughout all nuclei of the ventral posterior complex and show increased numbers in the small celled (s) region of VPM and in the VPI and VMb nuclei. Scale bar=750 μm. From material described in Rausell *et al.*[60]

VPL and VPM. Where parvalbumin cells are absent, as in VMb and VPI, only calbindin cells are found. Parvalbumin-rich zones are invariably associated with high metabolic activity, as reflected in dense histochemical staining for CO, while calbindin rich zones invariably show weak staining for CO. In VPM, calbindin-rich, CO-weak zones are insinuated between the parvalbumin-rich, CO-strong rods and expand as a relatively large (S) region along the medial edge of VPM, as well as into VMb and VPI which contain only calbindin cells. The calbindin cells of VPI extend up into VPL to become continuous with calbindin-only, CO-weak zones between the lamellae of more numerous parvalbumin cells. Of special note is the fact that as VPM and VPL narrow to their posterior poles, the calbindin-rich, CO-weak, parvalbumin-negative, S zone and the VMb and VPI nuclei expand as a large, calbindin-only region that forms the posterior nucleus (Po). This is intercalated between the ventral posterior, medial geniculate, limitans-suprageniculate and anterior pulvinar nuclei at the caudal pole of the thalamus.

3.2. Medial geniculate complex

The medial geniculate body is also a complex of nuclei: the ventral nucleus (MGv) which forms the principal relay to the primary auditory cortex, the dorsal nucleus, composed of anterodorsal (MGad) and posterodorsal (MGpd) subnuclei which project

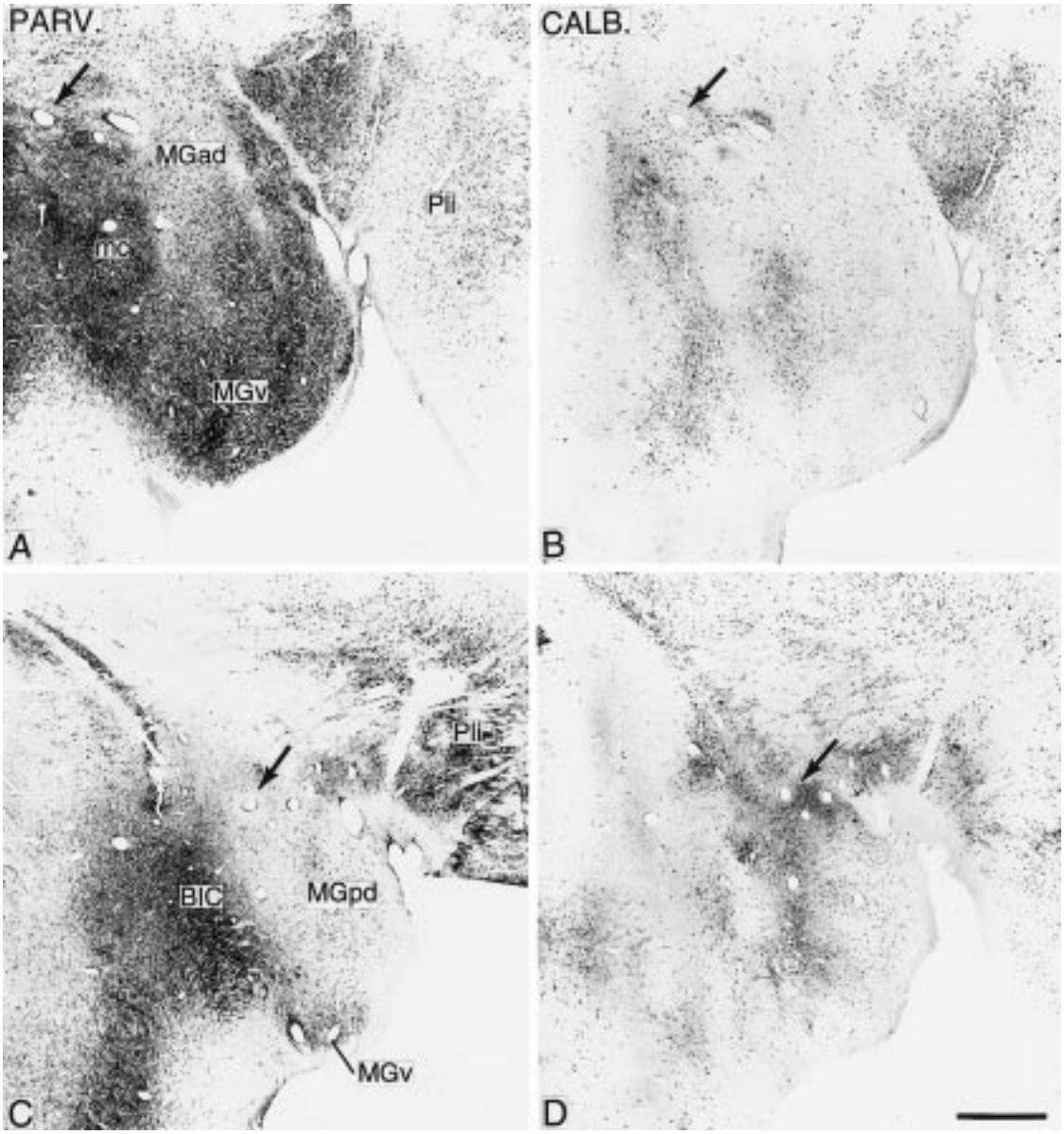

Fig. 3. Pairs of adjacent frontal sections at middle (A,B) and posterior (C,D) levels through the medial geniculate complex of a macaque monkey, showing the enrichment of parvalbumin cells in the ventral nucleus (MGv) and in parts of the magnocellular nucleus (mc), and the matrix of calbindin cells in these and in the anterodorsal (MGad) and posterodorsal (MGpd) nuclei. BIC, brachium of inferior colliculus; Pli, inferior pulvinar nucleus. Scale bar=500 μm. Arrows indicate same blood vessel. From material described in Molinari *et al.*[49]

to fields around the primary auditory cortex, and the magnocellular nucleus (MGmc) which has widespread cortical connections.[23,49] As in the ventral posterior complex, parvalbumin cells are found in local concentrations while calbindin cells form a matrix to the whole complex, showing complementary subnuclear increases in number where parvalbumin cells are absent (Fig. 3). Parvalbumin cells dominate MGv and here calbindin cells are at their fewest. In MGad, parvalbumin cells are still predominant but more calbindin cells are evident. On moving posteriorly from MGad into MGpd, parvalbumin cells fall off, until at the posterior pole of the complex, in the most posterior part of MGpd, only calbindin cells are present. Significantly, as with the S zone of VPM, the calbindin cells in the posterior part of MGpd extend without interruption across the border between MGpd and the adjacent inferior pulvinar nucleus (Pli) to become continuous with the larger population of calbindin cells found in Pli. In MGmc, there are interspersed islands of calbindin and parvalbumin cells. The large cells that give the nucleus its name are calbindin positive.[49]

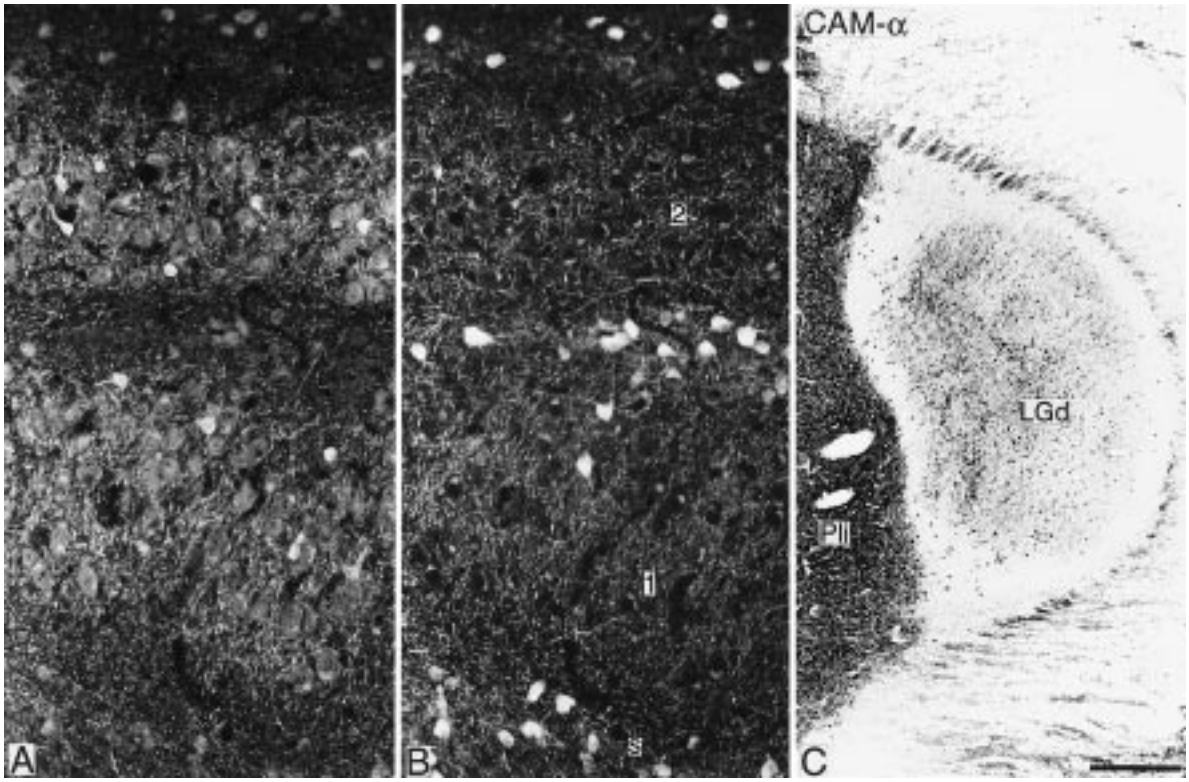

Fig. 4. (A,B) Fluorescence photomicrographs from the same microscopic field, showing parvalbumin-immunoreactive cells concentrated in two of the principal laminae (1,2) of the dorsal lateral geniculate nucleus (A, fluorescein immunofluoresence) and calbindin-immunoreactive cells restricted to the S laminae and interlaminar plexuses (B, rhodamine immunofluoresence). From material described in Jones and Hendry.[36] (C) Immunoperoxidase section showing the calbindin cells of the dorsal lateral geniculate nucleus, in this case labelled by immunoreactivity for alpha-typeII calcium/calmodulin-dependent protein kinase (CAM-α) extending across the border into the adjacent inferior pulvinar nucleus (Pli). From material described in Tighilet *et al.*[72] Scale bar=40 μm (A,B), 500 μm (C).

3.3. Dorsal lateral geniculate nucleus

The principal laminae (1–6) of the dorsal lateral geniculate nucleus (LGd) are dominated by parvalbumin cells, nearly all their relay cells being parvalbumin immunoreactive.[36] The smaller celled, S laminae (in the optic tract external to lamina 1) and similar cells located in the interlaminar plexuses between the principal laminae, are dominated by calbindin-immunoreactive cells. The calbindin cells can also be identified by co-localization of alpha-type II calcium/calmodulin-dependent protein kinase (CAMKII-α).[4,24,34,72] Although there is a superficial impression of true complementarity in the distributions of the parvalbumin and calbindin cells in LGd, calbindin cells, in fact, permeate the whole nucleus, insinuating themselves in small numbers among the parvalbumin cells of the principal laminae. As in the ventral posterior and medial geniculate complexes, the calbindin/CAMKII-α cells also extend beyond the confines of the LGd into adjacent nuclei. This is especially noticeable posteriorly where, as the LGd becomes enveloped in the enlarging Pli nucleus, calbindin/CAMKII-α cells extend uninterruptedly across the intervening medullary lamina, to become continuous with the larger population of similar cells in Pli (Fig. 4).

There is a size difference between calbindin and parvalbumin cells, the calbindin cells in all nuclei being significantly although not dramatically smaller in size. In the different regions of the ventral posterior complex, calbindin cells have a somal area of 180–200 μm^2 while parvalbumin cells have somal areas of 200–250 μm.[2,4,60] A similar size difference is found in the medial geniculate complex and in LGd.

In the dorsal thalamus of monkeys, calbindin- and parvalbumin-immunoreactive cells are thalamocortical or thalamostriatal relay cells and, with rare exceptions, neither of the calcium-binding proteins is expressed in the intrinsic GABAergic interneurons.[36] Parvalbumin is, however, expressed in the GABA cells of the outlying reticular nucleus.[36]

4. DIFFERENTIAL CORTICAL PROJECTIONS

When the cortical projections of the calbindin and parvalbumin cells in the three nuclei described above, are examined experimentally, two facts emerge: (i) regardless of the nucleus in which they lie, parvalbumin cells invariably project to middle layers (III–IV)

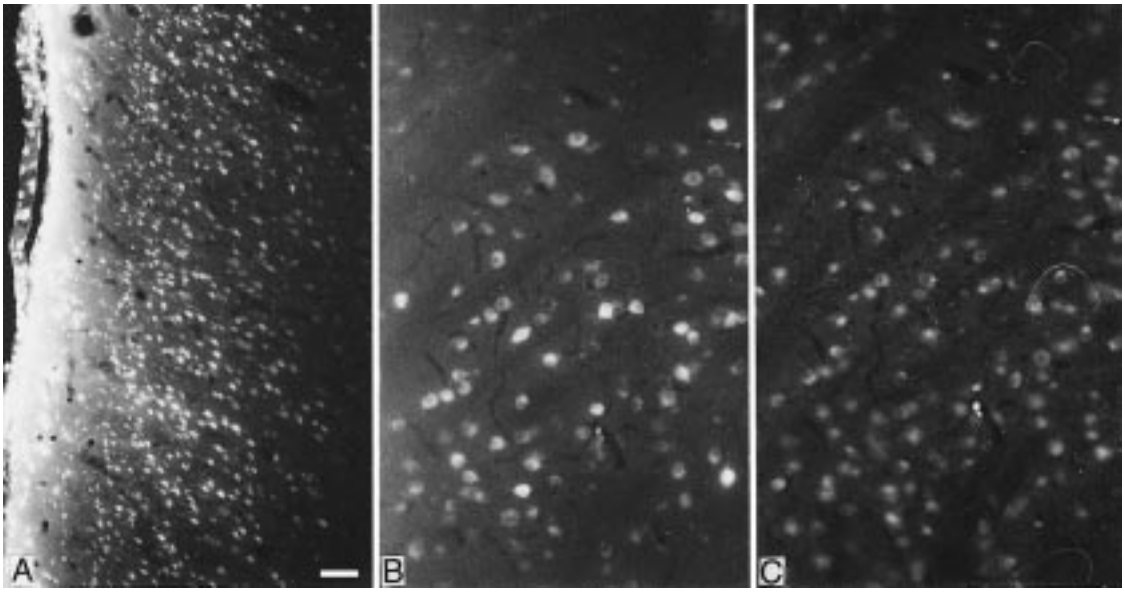

Fig. 5. (A) Application of the retrogradely-transported tracer, Fast Blue, to the surface of the cerebral cortex results in penetration into superficial layers and leads to retrograde labelling of only calbindin-immunoreactive cells in the thalamus. (B,C) Fluorescence micrographs from the same microscopic field, showing neurons labelled by retrogradely-transported Fast Blue (B) and immunoreactive for calbindin (C) after an injection of the type shown at left. From material described in Rausell *et al.*[60] and Rausell and Jones.[62] Scale bars=100 μm (left), 50 μm (right).

of the cortex while calbindin cells project to superficial layers, (I, II and probably upper III); (ii) the parvalbumin cells project in a highly topographically-ordered fashion to a single cortical field, while calbindin cells project more widely, unconstrained by architectonic or functional boundaries between fields.

The evidence for the layer-specific projections of the two classes of cell comes from experiments in which retrogradely-transported fluorescent dyes were either applied to the surface of the cortex, affecting layers I–II and possibly upper layer III, or injected via micropipettes into the middle layers.[22,24,49,60,62] Applications of dyes to the surfaces of the somatosensory, auditory or visual areas of the cerebral cortex invariably resulted in retrograde labelling only of calbindin cells in the ventral posterior, medial geniculate or lateral geniculate nuclei (Fig. 5). Deeper injections of dye led to retrograde labelling of a majority of parvalbumin cells, but with a few calbindin cells, probably because of involvement in the injections of axons of calbindin cells ascending to superficial layers. The relative size ranges of the thalamic cells retrogradely labelled from superficial applications or middle layer injections of dye, also reflects the differential labelling of the two classes of cell.[60] In the MGmc nucleus where its groups of parvalbumin cells are labelled by deeper injections and its groups of calbindin cells by superficial applications, the differential projections have been confirmed by single fibre tracing.[23]

In addition to layer-specific projections, the results of these studies show that calbindin cells project more widely and diffusely on the cortex than parvalbumin cells. Tracer applied to the surface of the somatosensory cortex invariably labels calbindin cells not only in VPL or VPM but also in the adjacent VPI, Po and anterior pulvinar (Pla) nuclei, and even in the ventral lateral posterior (VLp) nucleus which forms the principal thalamic relay to the motor cortex. Injections of middle layers, by contrast, label parvalbumin cells only in the somatotopically related part of VPL or VPM. Similar experiments involving the auditory cortex show widespread projections of calbindin cells to fields surrounding the primary auditory area, while parvalbumin cells in MGv project topographically to the primary area only[49] (Fig. 6). In the LGd it has been known for some time that cells in the principal layers project only to area 17 while those of the S laminae and interlaminar zones project more widely: to areas 17 and 18 and possibly beyond.[75,78]

5. DIFFUSE AND FOCUSED SUBCORTICAL INPUTS

Just as the calbindin and parvalbumin cells form diffuse and more specifically organized pathways to the cerebral cortex, respectively, so their subcortical inputs appear to have similar characteristics. This is particularly evident in the ventral posterior and medial geniculate nuclei (Figs 6, 7). In the ventral posterior complex, the parvalbumin-rich VPL and VPM nuclei are the sole termini of the medial and trigeminal lemnisci which end in them in the well-known somatotopic order. The lemniscal fibres are all parvalbumin positive. By contrast, the spinothalamic and spinal trigeminothalamic pathways

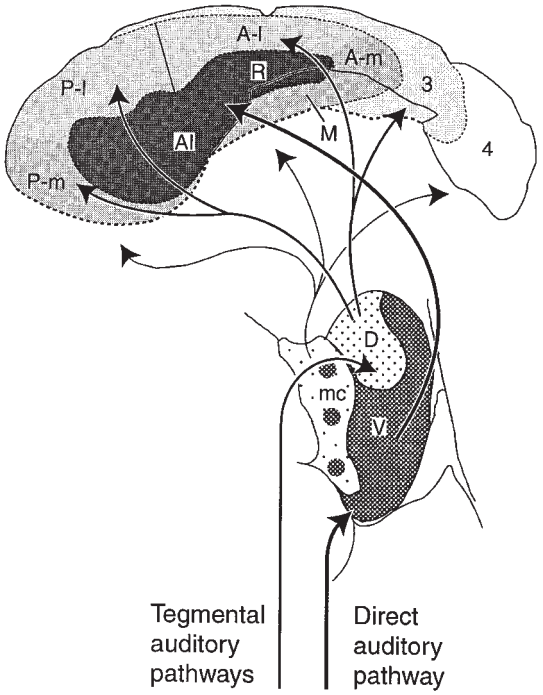

Fig. 6. Schematic view of the organization of the input-output connections of the medial geniculate complex. The parvalbumin-rich, ventral nucleus (V) receives the terminals of the most direct, oligosynaptic pathway from the contralateral ventral cochlear nucleus and projects to the primary auditory cortical areas (AI and R) which form a parvalbumin-rich core on the surface of the supratemporal plane. The dorsal nuclei (D), in which the calbindin matrix predominates, receive inputs predominantly from less direct auditory pathways located in the lateral midbrain tegmentum and project to auditory cortical areas surrounding the primary core (A-l, A-m, M, P-l, P-m). These areas display less dense parvalbumin immunostaining. Areas 3 and 4 beyond the surround display very weak or absent parvalbumin immunostaining. The magnocellular nucleus (mc) receives inputs from a variety of sources, not all of them auditory. It contains a calbindin matrix with islands of parvalbumin cells and projects widely upon all auditory and adjacent fields. Modified from Molinari *et al.*[49]

terminate in widespread, dispersed bursts of terminals that not only occur throughout the whole complex but also extend beyond VPL/VPM, VMb and VPI into adjacent nuclei such as VLp, Pla, Po and central lateral nucleus (CL). Of special note is the fact that the bursts of terminals are concentrated in the calbindin-rich, CO-weak, parvalbumin-deficient zones of VPL and VPM and in other nuclei or parts of nuclei characterized by these same features (Figs 8, 9). It is not yet clear if all the arriving subcortical fibres are calbindin positive.[60]

In the medial geniculate complex, an identical arrangement is seen. The parvalbumin-rich, MGv and MGad nuclei are the recipients of tonotopically-ordered inputs from the central nucleus of the inferior colliculus which represents the most direct ascending pathway from the contralateral cochlea. The afferent fibres are all parvalbumin positive.[49] The calbindin-rich, parvalbumin-weak regions of MGpd are innervated by less direct auditory pathways which ascend in the lateral midbrain tegmentum and terminate in dispersed fashion throughout most of the dorsal nuclei. These fibres are all calbindin positive. MGmc receives both parvalbumin and calbindin fibres from multiple sources. The calbindin-rich dorsal nuclei can be viewed as relays for less specifically organized information to reach superficial layers of the cerebral cortex over relatively wide areas: although the tegmental inputs to these nuclei retain some of the quality of the sensory pathway with which they are associated, they have less precise submodality properties. Cells in the dorsal medial geniculate nuclei, for example, show less sharp frequency tuning than cells in MGv, fatigue more readily, and are affected at longer latency by auditory stimuli.[69]

The situation is less clear in LGd, mainly for lack of information. Parvalbumin and calbindin fibres of retinal origin clearly innervate the nucleus[36] but it is not yet known if they end on the largely separate calbindin and parvalbumin geniculate relay cells. The parvalbumin-rich principal laminae are the relays for retinotopically ordered inputs from the colour-coded (P) and broad band (M) groups of retinal ganglion cells.[26,67] Inputs to the S laminae and interlaminar zones come from both the superficial layers of the superior colliculus[20,21] and the retina.[38] It is noteworthy that the tectal inputs extend uninterruptedly into the S laminae and interlaminar zones from a series of patchy terminal foci in the Pli nucleus, not unlike the diffuse spread of spinothalamic and tegmental inputs across nuclear borders in the ventral posterior and medial geniculate complexes. There is also some older evidence for extension of retinal terminations from the S laminae into the Pli.[6] The retinal inputs to the S laminae and interlaminar zones have been likened, by anatomical analogy, to the W cell inputs to the LGd of the cat[17,24] although there is no physiological evidence for this in the monkey. If the analogy can be sustained functionally, these inputs will share some of the features of the spinothalamic and tegmental inputs to their respective nuclei, namely less fine topographic organization, less easily defined receptive fields and sluggish or easily fatigued responses.

6. THE INTRALAMINAR AND OTHER NUCLEI

The idea of a matrix of diffusely and superficially projecting calbindin cells driven by less precise subcortical inputs, overlain by a core of topographically-ordered parvalbumin cells projecting to middle layers in an area-specific manner and driven by more precise subcortical inputs, seems compelling for the ventral posterior, medial geniculate and lateral geniculate nuclei. What about other nuclei of the thalamus, especially the intralaminar nuclei? Based on the evidence of a striatal projection, the

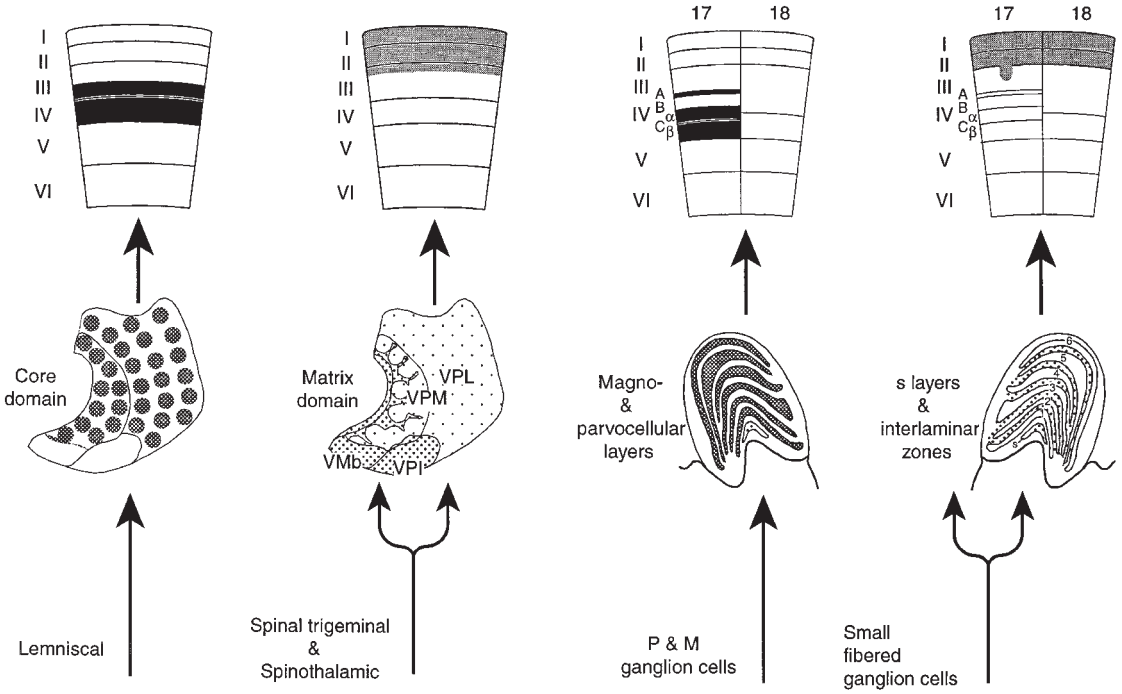

Fig. 7. (Left) Schematic view of the organization of input-output connections of the ventral posterior nuclear complex. Medial and trigeminal lemniscal fibres terminate in the parvalbumin-rich cores of the VPL and VPM nuclei, the cells of which project to layers IIIB and IV of the somatosensory cortex. Spinothalamic and spinal trigeminal fibres terminate more diffusely throughout the complex and are concentrated in regions in which the calbindin matrix is enriched, namely the S region of VPM and the VMb and VPI nuclei. The calbindin cells project to superficial layers of the somatosensory and adjacent areas of the cortex. After Rausell and Jones[61,62] and Rausell *et al.*[60] (Right) Schematic view of the organization of input-output connections of the dorsal lateral geniculate nucleus in macaques. The parvalbumin-rich principal laminae receive inputs from the wavelength-specific, P, or broad band, M, retinal ganglion cells and project to subdivisions of layer IV of area 17 only. The calbindin-rich S layers and interlaminar plexuses are innervated by other ganglion cells, , and by the superior colliculus (not shown). The tectal and possibly the retinal inputs extend into the adjacent inferior pulvinar nucleus. The calbindin cells project to superficial layers of both areas 17 and 18, including the CO-rich blobs of the former.

intralaminar nuclei in monkeys can now be considered to incorporate the magnocellular ventral anterior nucleus and parts of the principal ventral anterior nucleus, anteriorly, and the limitans-suprageniculate (Li-SG) and magnocellular medial geniculate nuclei, posteriorly.[28,35] Within the intralaminar nuclei, as a whole, there are some zones in which calbindin cells and parvalbumin cells comingle; in others they form more or less completely segregated clusters, resembling the zones of VPM and VPL; this is seen in the MGmc, Li-SG and CL nuclei. In certain nuclei, e.g., the centre médian and parafascicular, parvalbumin cells are present in overwhelming numbers, to the virtual exclusion of calbindin cells, while in others e.g., the CL nucleus, calbindin cells predominate over parvalbumin cells (Fig. 10).[36] We do not yet know if both calbindin and parvalbumin cells project to the striatum but it is clear from the nuclei so far sampled (e.g., the MGmc alluded to above), that calbindin cells in the intralaminar nuclei project widely to superficial layers and parvalbumin cells more locally to middle layers of the cerebral cortex. We can, thus, see the intralaminar complex as containing some nuclei with mixed subpopulations of cells having middle layer and superficial cortical projections and other nuclei in which the two subpopulations are largely segregated. The parallels with the three sensory relay nuclei are evident. Within every nucleus of the whole enlarged intralaminar complex, we would anticipate that striatally projecting cells would form a further, much larger subpopulation, since most of the evidence is against the majority of striatally projecting cells having collateral projections to the cerebral cortex.[45,46]

Turning to other dorsal thalamic nuclei, outside the confines of the intralaminar or principal sensory relay complexes, a distribution of calbindin and parvalbumin cells similar to that in the principal sensory relay and intralaminar nuclei appears to exist.[36] All nuclei have a matrix of calbindin cells; some nuclei, such as VLp, which receives cerebellar inputs and projects to the motor cortex, contain a predominance of parvalbumin cells; others such as the anterior ventral lateral nucleus (VLa), which receives pallidal inputs and projects mainly to premotor cortex, or Pli which receives tectal inputs

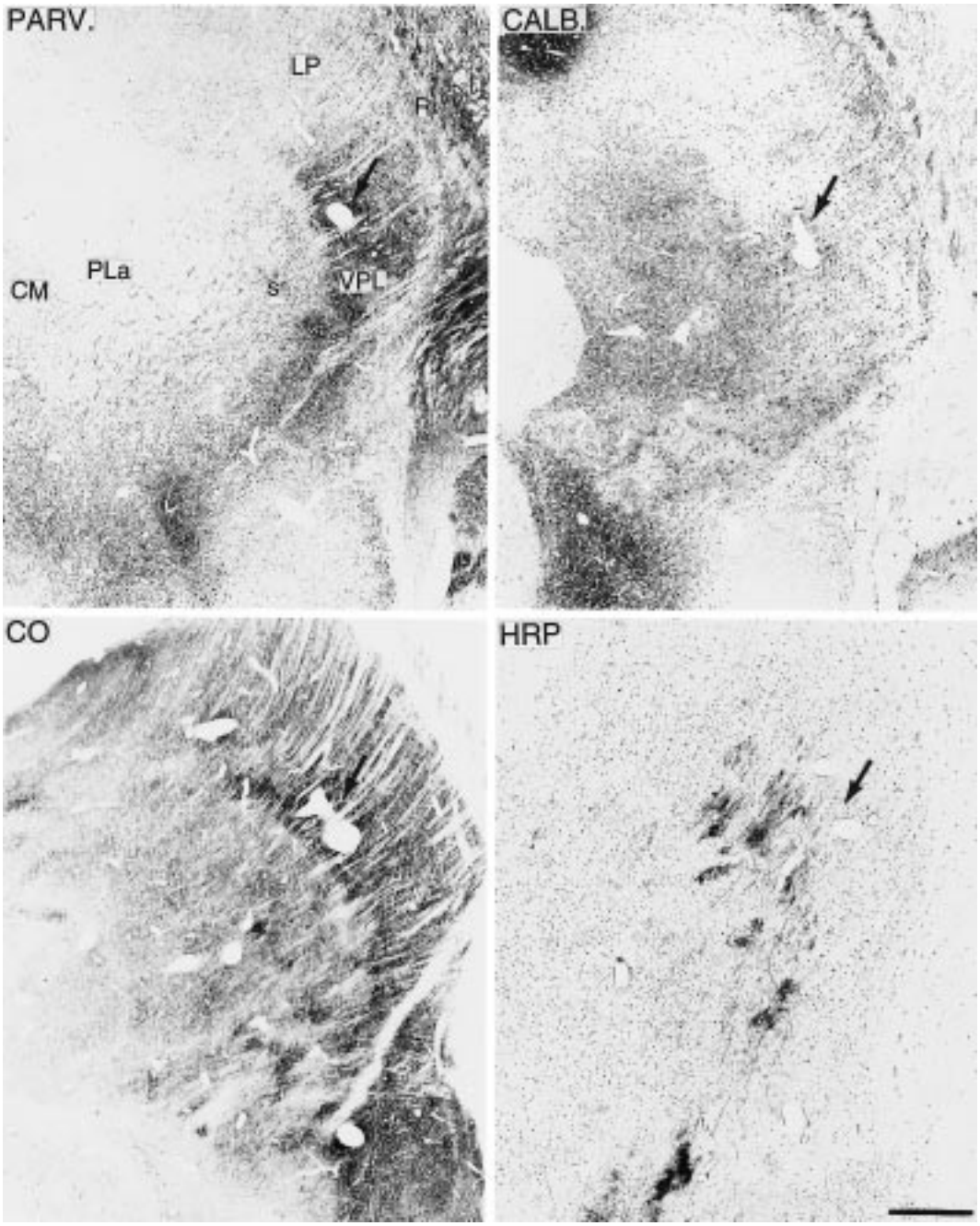

Fig. 8. Frontal sections towards the posterior pole of the VPL nucleus of a macaque monkey, stained for parvalbumin (PARV.) or calbindin (CALB.) immunoreactivity, for cytochrome oxidase (CO), or for spinothalamic fibre terminations labelled with wheat germ agglutinin-conjugated horseradish peroxidase (HRP). These shown the expansion of the parvalbumin-weak, CO-weak but calbindin-rich matrix (S) in the region of the posterior nucleus and the concentration of spinothalamic terminations in the matrix. From material described in Rausell *et al.*[60] Scale bar=500 μm. Arrows indicate the same blood vessel.

and projects to parts of the extrastriate cortex, contain approximately equal numbers of calbindin and parvalbumin cells; yet others e.g., Pla, which receives ill-defined inputs and projects to anterior parietal cortex, essentially contain calbindin cells only (Fig. 10). The inference to be drawn from all this is that the projections of those thalamic nuclei, intralaminar and non-intralaminar, that contain a majority of parvabumin cells, are focused on middle layers of individual cortical areas while those of other nuclei that contain a majority of calbindin cells, are spread more diffusely across superficial layers of a number of adjacent cortical areas. Where populations are more evenly mixed, the projections will be to both superficial and middle layers. The presence of diffusely-projecting calbindin cells and area-specific

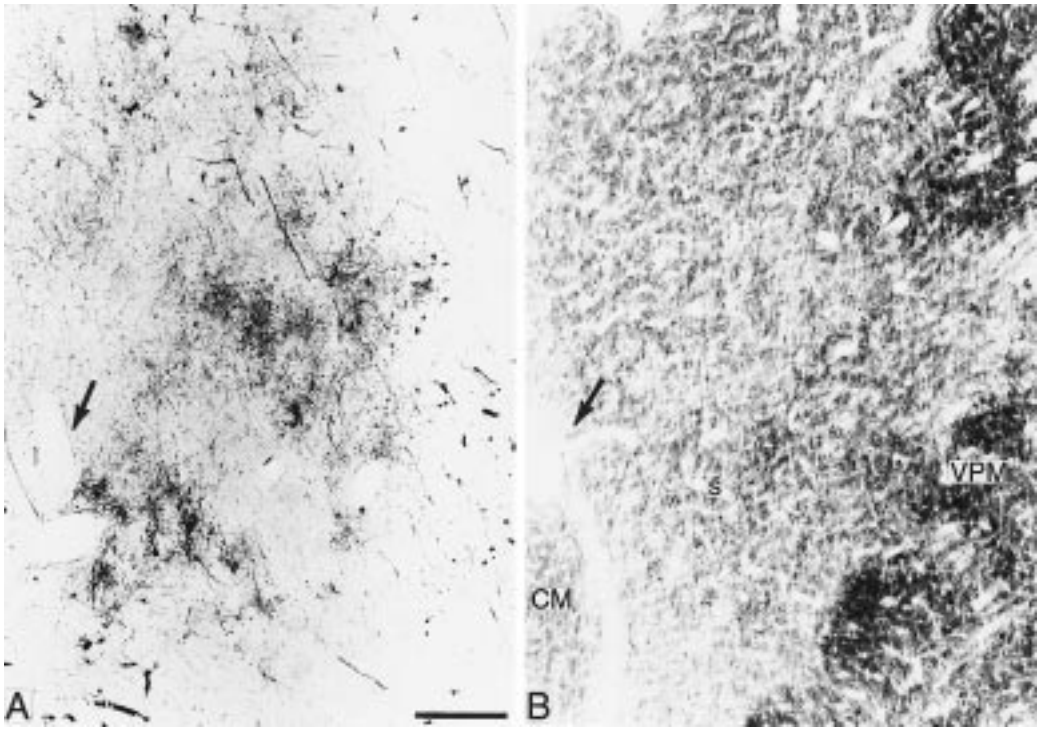

Fig. 9. Adjacent sections through the middle of the VPM nucleus, showing anterogradely-labelled terminations of fibres arising from the caudal nucleus of the spinal trigeminal complex (A), ending in relation to the CO-weak, calbindin-rich s region of the nucleus, avoiding the CO-stained patches in which parvalbumin cells are concentrated (B). From material described in Rausell and Jones.[62] Scale bar=100 μm.

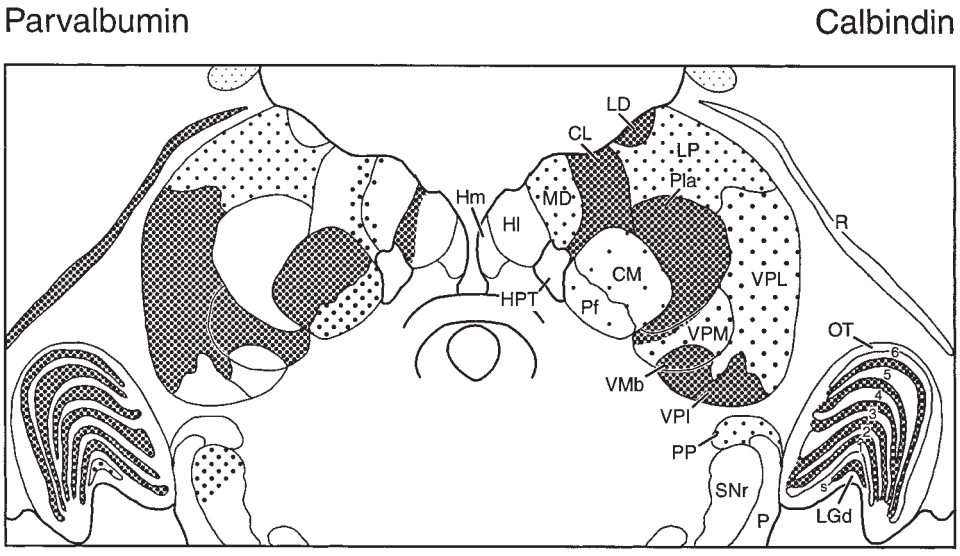

Fig. 10. Distribution of parvalbumin- and calbindin-immunoreactive cells in a frontal section through the middle of a macaque thalamus. In the intralaminar nuclei, parvalbumin cells dominate the centre médian and parafascicular nuclei but are uncommon in the central lateral nucleus. Calbindin cells dominate the central lateral nucleus but are uncommon in the centre médian and parafascicular nuclei. Note also the opposite reciprocity in the anterior pulvinar nucleus (Pla). Redrawn from Jones and Hendry.[36]

parvalbumin cells in the same nucleus probably holds the key to resolving disagreements based on retrograde anatomical labelling, as to what is ''the'' cortical projection of a particular thalamic nucleus, since the number of nuclei containing retrogradely-labelled cells will be a function of the extent of involvement of superficial layers in a cortical injection of tracer.

7. FUNCTIONAL CONCEPTS

Interactions between the thalamus and cerebral cortex are the foundations upon which the state-dependent activities of the forebrain are built, and recent studies clearly indicate the necessity of engaging the whole thalamus in switching between conscious states.[8–12,43,68,69,70] All theories related to the issue of how large numbers of thalamic cells can be recruited into collective action, depend upon some form of intrathalamic connection that extends across nuclear borders. For the low frequency oscillations of thalamic and cortical cells, in the delta and spindle frequency ranges, that are the accompaniments of slow-wave sleep and which depend upon recurrent burst firing of relay cells as they recover from reticular nucleus-imposed inhibition,[2,27,29,30,41,42,47,74] connections between adjacent reticular nucleus cells[14,77] may be sufficient to ensure spread of the inhibitory influence across nuclei,[47] although corticothalamic connections play a prominent role in synchronizing the oscillations.[8–12] For higher frequency oscillations in the 40 Hz range, which occur during conscious attention and when propagated across thalamic nuclei and cortical areas may serve to bind together all those cortical events essential to the act of perception, it has been thought necessary for a cortical area, activated by a sensory stimulus, to gain access first to an intralaminar nucleus and thence, via intrathalamic connections between intralaminar nuclei and their diffuse projections to the cortex, to other cortical areas.[43] The present evidence for the existence of diffusely-projecting relay cells in all nuclei (with greatly enhanced numbers in some), makes it unnecessary to invoke the intralaminar nuclei as the sole contributors to the recruitment of widespread cortical areas. They are by no means excluded from this role, but the diffusely projecting cell of the intralaminar nuclei are components of a much more widely distributed thalamic matrix. It also makes it less imperative to invoke inter-intralaminar connections (which are controversial) in this process. Moreover, it renders inconsequential the seeming paradox that the primary visual and auditory areas of the cortex, unlike other cortical areas, do not project to the classical intralaminar nuclei.

One can envisage corticothalamic feedback from a cortical area to the calbindin cells of its thalamic relay nucleus being used to engage, via the diffuse projections of the calbindin cells, other adjacent cortical areas. These areas, in turn, would feed back to the calbindin cells of their thalamic relay nuclei, and so on, leading to dispersion of activity across the whole cortex. The process of recruiting thalamic nuclei would be greatly facilitated by the presence of corticothalamic fibres returning to thalamic nuclei other than that from which an area receives its principal thalamic input. The majority of corticothalamic fibres arise from cells in layer VI of the cortex and return to the relay nucleus proper to the area in which they lie. Layer VI of area 17, for example, returns corticothalamic fibres to the LGd. Other corticothalamic fibres, arising from cells in layer V, project to other thalamic nuclei, in the case of the visual cortex reaching parts of the pulvinar,[63] in the case of the primary auditory cortex reaching the dorsal and magnocellular medial geniculate nuclei,[52,54] and in the case of the primary somatosensory area reaching parts of the intralaminar nuclei and the anterior pulvinar nucleus.[33,58] It seems particularly apposite that these are thalamic nuclei or subnuclei that are especially enriched in superficially-projecting, calbindin cells.

8. NON-PRIMATE SPECIES?

The view presented here is largely based upon researches carried out in simian primates in which the duality of the calbindin- and parvalbumin-immunoreactive relay cells, their often complementary distributions, and the lack of expression of the two calcium-binding proteins in the intrinsic GABAergic neurons, makes the case for chemo-specific diffuse and specific thalamocortical relay systems particularly easy to draw. Can the idea of the two systems be extended to other non-primate species, such as cats and rodents, the former of which has been one of the mainstays of thalamocortical research for at least half a century?

To extend the principle to cats and other common experimental animals such as rodents, solely on the basis of immunocytochemical staining for the calcium-binding proteins would be to invite error and cause confusion. The line between the cell-specific expression of parvalbumin and calbindin is far less clearly drawn in these species than in monkeys. Although studies on cats and rats have been far less systematic than those conducted on monkeys, it is clear that in cats the predominant cortically projecting cells are calbindin-immunoreactive while parvalbumin is expressed in intrinsic GABAergic cells as well as in those of the reticular nucleus.[3,13,50,69] It is not clear whether parvalbumin is also expressed in relay cells but this does not appear to be the case in the intralaminar nuclei.[50] In the medial geniculate complex of rabbits, there is evidence for a complementarity in the distribution of calbindin and parvalbumin akin to that seen in monkeys.[15] In rats,[7,69] calbindin-immunoreactive cells also appear to dominate the dorsal thalamus, parvalbumin cells being confined to the reticular nucleus. But the cells of many dorsal thalamic nuclei in the rat lack immunoreactivity for either calcium-binding protein. (Some express a third calcium-binding protein, calretinin[76]) It would be wrong to assume, however, from a lack of comparable chemo-specificity that the organization of the feline and rodent thalamus is fundamentally different from that of the primate. Superficially- and middle layer-projecting thalamocortical cells, and thalamostriatal cells are obviously

present in both species.[1,5,39,40,48,50,55–57,59,66] What appears to be different is the expression of the calcium-binding proteins. Although the species-specific patterns of expression of the two best known calcium-binding proteins, calbindin and parvalbumin, may hold some fundamental truth about the biochemical and cellular properties of those thalamocortical relay neurons that express them, this truth is currently unrevealed to us. For the purposes of the case being presented here, it is largely irrelevant, the differential immunostaining in monkeys merely providing a convenient means of dissecting out the two thalamocortical projection systems. What is more important to ask is whether two similar, diffuse and focused thalamocortical systems are present across species? Of greater import than the species-specific patterns of calcium-binding protein expression, may be species differences in the relative proportions of diffuse and focused projections.

The latter issue has not been addressed and it is doubtful that it is readily amenable to investigation. What is known, however, is that thalamocortical relay cells in cats and rodents do fall into diffuse, superficially-projecting and focused, middle layer-projecting types, and that thalamostriatal cells form a third class of thalamic projection neuron located in the environs of the internal medullary lamina and in nuclei comparable to the striatally-projecting nuclei not traditionally included in the intralaminar system in monkeys.[5,25,45,64,65] To take but a few examples: the A layers of the dorsal lateral geniculate nucleus of the cat contain cells projecting in a topographically ordered manner to middle layers of areas 17 and/or 18, while cells in the C layers project widely to superficial layers of these and surrounding areas;[39] the ventral posterior nucleus of the rat projects in topographic order to middle layers of the somatosensory cortex while the adjoining posterior medial nucleus projects to superficial layers of the same area;[69] in cats, small cells forming a matrix to the ventral posterior nucleus project to superficial layers of the somatosensory cortex while larger cells project in the classic, topographically ordered manner to middle layers;[1,59] a similar duality is found in the medial geniculate nucleus.[48] Intralaminar cells are described as projecting to superficial cortical layers in cats[40,65] and to deep[25] or superficial layers in rats. The newest evidence in cats shows the presence of two sets of cortically-projecting intralaminar cells, one with focused middle-layer projections[50] exactly comparable to those in monkeys, although all the projecting cells appear to be calbindin positive. The major outflow of the intralaminar nuclei in both species is, again, to the striatum[46] with little or no collateral branching to the cerebral cortex.

Although the data are less complete in non-primate species, these several examples suggest the likelihood that non-primates also possess a matrix of diffusely and superficially projecting, smaller thalamocortical cells upon which a core of more specifically projecting relay cells is imposed in both relay and intralaminar nuclei. This dual thalamocortical system may, therefore, be fundamental to all species. The differential expression of the calcium-binding proteins in the two systems of relay cells in monkeys may be but an evolutionary quirk that has permitted the two systems to be anatomically dissected. The challenge for the future will be in the testing of the several facets of the hypothesis presented here by selectively targeted experiments.

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