ELSEVIER

Brain Research Reviews 28 (1998) 286–308

BRAIN RESEARCH REVIEWS

Full-length review

The organization of corticothalamic projections: reciprocity versus parity

Martin Deschênes *, Pierre Veinante, Zhong-Wei Zhang

Centre de Recherche Université Laval-Robert Giffard, Hôpital Robert Giffard, 2601 de la Canardière, Beauport, Québec, Canada G1J 2G3

Accepted 9 June 1998

Abstract

All neocortical areas receive inputs from and project back to the thalamus. It is often said that the corticothalamic projections are organized in a way that reciprocates the spatial distribution of thalamocortical pathways. The present review examines to what extent this rule of reciprocity is actually supported by the most recent neuroanatomical data, particularly those relating to the central organization of the vibrissal sensory system in the rat. A critical survey of previous studies is made and new results are presented concerning the fine-grained organization of corticothalamic projections in this sensory system. Together, prior results and the present set of new data confirm the existence of both, reciprocal and nonreciprocal patterns of corticothalamic connectivity. This conclusion leads us to propose that the spatial organization of corticothalamic connections complies with a more fundamental rule, the rule of parity, from which reciprocity follows as a general, but not obligatory consequence. The rule of parity states that the distribution of corticothalamic projections across and within the thalamic nuclei is determined by the branching patterns of the different classes of prethalamic afferents. The anatomical, developmental and physiological consequences of this rule are discussed. The rule of parity suggests that, according to the behavioral context, both prethalamic and corticothalamic pathways may function in a feedback mode.

Keywords: Vibrissal sensory system; Corticothalamic feedback; Thalamocortical projection; Layer 6 cell; Thalamic relay cell; Reciprocity

Contents

* Corresponding author. Fax: +1-418-663-8756; E-mail: martind@microtec.net

0165-0173/98/$ - see front matter
PII: S0165-0173(98)00017-4

1. General introduction

This article bears on the organization of corticothalamic (CT) pathways. Our main objective is to examine whether CT projections that arise from layer 6 of the neocortex actually reciprocate the thalamocortical projection systems. The notion of reciprocity was first introduced in neuroanatomy by Diamond et al. [27] to describe the spatial distribution of the CT projections from the auditory cortical areas in cats. Since the publication of that paper, this topographic reciprocity has been supported by such a large number of experimental data that one sometimes considers that exceptions to this rule just await the verdict of time. The physiological counterpart of reciprocity is the notion of feedback, which is currently used to comment on the functional significance of CT systems. Most researchers in the field, however, will recognize that in spite of the numerous experiments initiated along this line of thought, the physiological role of CT systems still remains an enigma. Initially, the principle of reciprocity was proposed as an organization rule of the anatomical links between thalamic nuclei and cortical areas. The question is whether this rule is to be considered merely as a useful descriptor of thalamocortical relationships or as a true operational principle, whereby the connections established by thalamic cells in the cortex specify the connectivity patterns of CT neurons. Are CT cells within a cortical column committed to make connections with, and only with, the relay cells that project to the same column? The present review addresses this issue with reference, in particular, to the rat vibrissal sensory system.

2. The principle of reciprocity

The principle of reciprocity states that a cortical area returns axons to the thalamic nucleus from which it receives afferents [27]. As schematized in Fig. 1, if cortical area A receives input from nucleus X, then, area A projects back to nucleus X. If area A receives inputs from nuclei X and Y, then area A returns axons to both nuclei X and Y. Implicitly, the principle of reciprocity rules out the possibility that cortical area A, for instance, might project to nucleus Z from which it does not receive afferents.

Soon after the introduction of the axonal transport techniques in neuroanatomy, it became clear that this principle also applied to small aggregates of relay cells within the sensory specific thalamic nuclei and their corresponding projection columns in the cortex. Even in association and intralaminar thalamic nuclei, where cells that project to a given cortical area are more dispersed or form separate cellular aggregates, reciprocal patterns of CT connectivity were found. The question naturally arises as to whether the principle of reciprocity also holds at a unitary level: Does any CT cell project back to all those thalamic cells from which it receives a direct synaptic input? A precise answer to this question still escapes

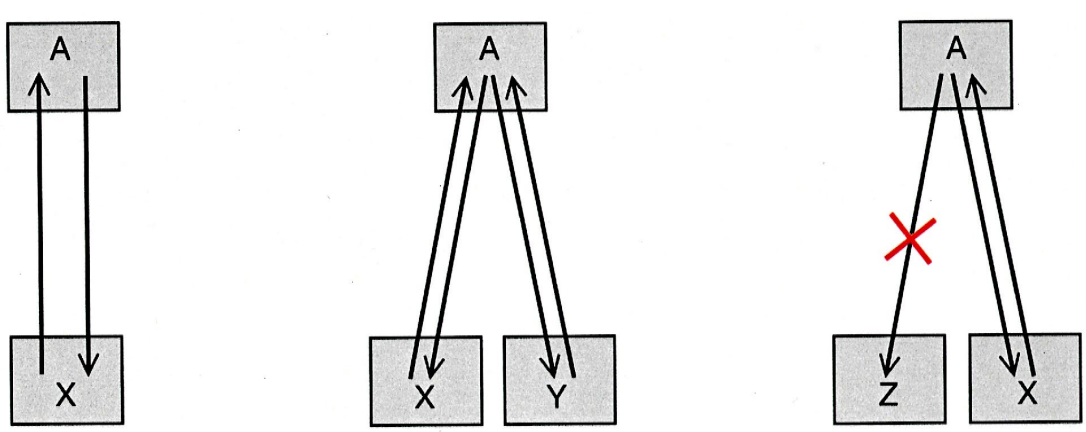


Fig. 1. Schematic illustration of the principle of reciprocity. Boxes X, Y and Z represent different thalamic nuclei and box A represents a cortical area.

present technical capabilities. What recent single-cell labeling studies clearly showed, however, is that each of the CT cells of a cortical column reciprocates only part of the connections received by the whole column. As far as it goes, then, these results do not actually dismiss the principle of reciprocity, but they suggest that the issue is more complex than what was previously thought.

Over the years, few studies reported data that seriously challenged the rule of reciprocity. Two cases in point are, for instance, the apparent lack of feedback projections from the visual areas 17 and 18 to the central lateral nucleus in the cat [23] and the existence of bilateral CT projections (see Section 5.5). Likely because these cases involve connections with the 'nonspecific' part of the thalamus, they were generally considered more as exceptions than as serious challenges to the rule. In other studies, however, zones of nonreciprocity were also found in the sensory specific nuclei such as the medial geniculate body of the rat [109] and the ventrobasal complex of the mouse [41]. Although it is always possible to raise methodological issues to limit the significance of these results, they nevertheless contribute to cast doubt on the idea that reciprocity is actually the organizational principle of the connections between the cortex and thalamus.

3. The vibrissal sensory system of the rat

The rodent somatic sensory system is characterized by a prominent representation of the mystacial vibrissae (see Fig. 2). On each side of the rat snout, there are five horizontal rows of whiskers (A, B, C, D and E) which form an orderly array of low-threshold mechanoreceptors. Each peripheral fiber innervating these mechanoreceptors responds to only one vibrissa and, centrally, the arrangement of the vibrissal pad is maintained in arrays of cellular aggregates referred to as barrelettes (brainstem), barreloids (thalamus) and barrels (cortex). These arrays are readily revealed in sections stained for the mitochondrial enzymes succinic dehydrogenase or cytochrome oxidase.

Brainstem nuclei that receive vibrissal primary afferents include the principal trigeminal nucleus (Pr5) and all subdivisions of the spinal trigeminal complex (Sp5). Each of these (sub)nuclei contributes axons to the trigeminothalamic tract, but the main stream of ascending fibers arises from the Pr5 and the interpolar division of the Sp5 (Sp5I). Trigeminothalamic fibers innervate the ventral posteromedial (VPm), posterior group (Po) and intralaminar nuclei of the contralateral thalamus, and each of these nuclei projects to the somatosensory cortical areas.

The rat primary somatosensory cortex (S1) comprises two intercalated cytoarchitectonic divisions. The granular zone, referred to as the barrel field, is characterized by dense cellular aggregates in layer 4. The interbarrel septa and regions surrounding the barrel field exhibit a low cell density in layer 4 and form together the dysgranular zone. The caudomedial part of S1, where barrels are especially prominent, contains the mystacial vibrissae representation.

4. Thalamocortical projections to S1

Since the mid-seventies, axonal transport techniques have provided a wealth of information about the areal and laminar distributions of thalamocortical projections [40,45]. However, our knowledge of these projections at a single-cell level remains limited to the arborization patterns of the relay cells of a few specific nuclei. In the case of the association and intralaminar nuclei, this type of information is virtually absent.

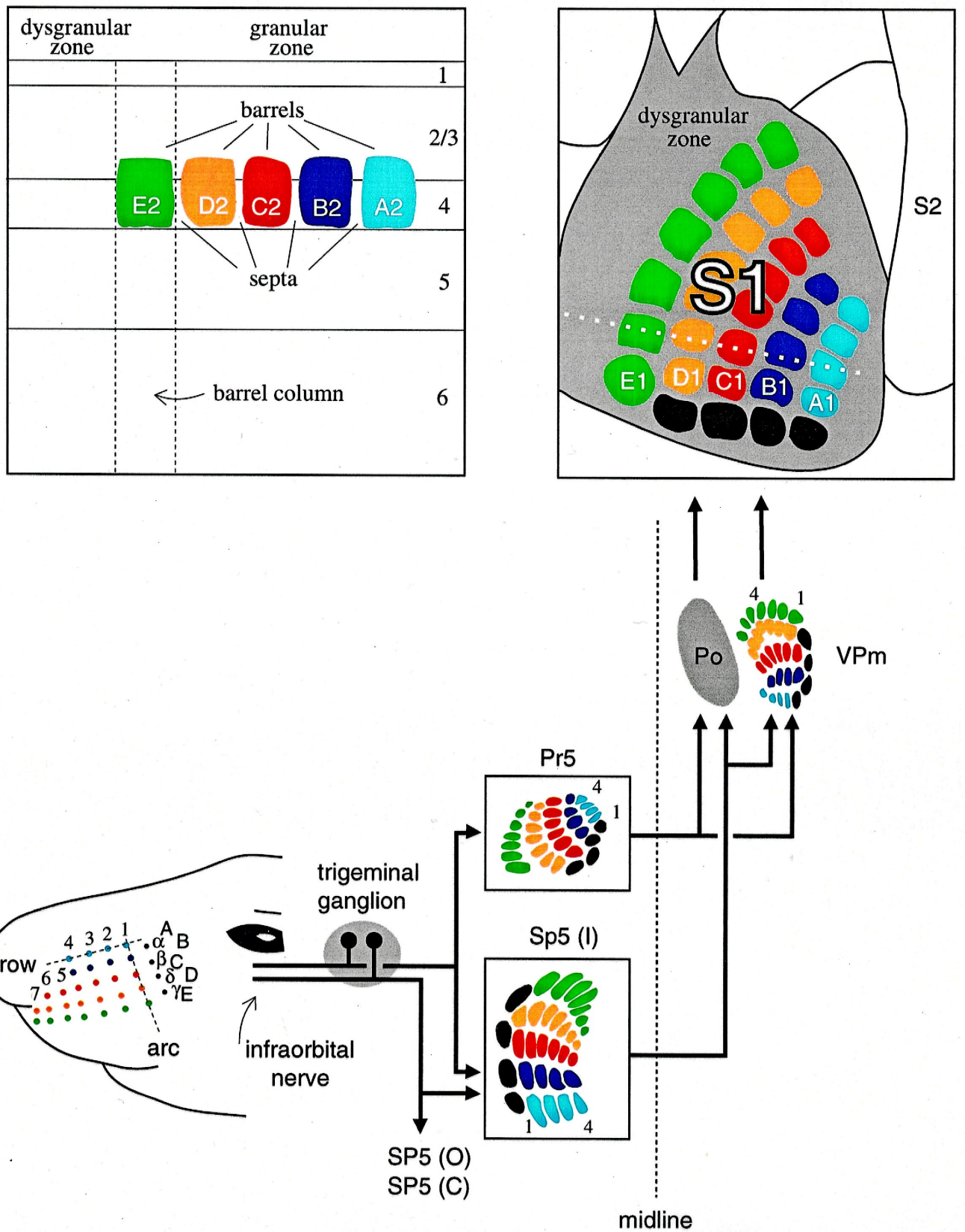
Thalamic afferents to area S1 in the rat arise principally from three thalamic territories: the VPm, the Po and the intralaminar nuclei (central lateral (CL), paracentral (Pc) and central medial (CeM)). The ventral medial nucleus (VM) also provides input to the rat S1 area, but this projection seems to involve a small number of cells that project principally to layer 1 [40]. Finally, a small number of neurons were reported labeled in the ventral lateral nucleus (VL) and the medial division of the medial geniculate body (MGm) after injection of fluorescent tracers in the posteromedial barrel field [76]. The precise topography of VM, VL and MGm afferents in S1 remains unknown.

4.1. Projections from the ventral posteromedial nucleus

Axons from the VPm innervate the barrel area where they form discrete puffs of terminals in the upper part of layer 6 and in layers 3–4 [3,11,21,44,50,51,64,110]. No evidence has been yet provided of a VPm projection to the dysgranular zone of S1. The VPm projection is extremely precise and establishes a one to one relationship between thalamic barreloids and cortical barrels [2,11,21,56]. When extra-barreloid retrograde labeling was reported after the

Fig. 2. Schematic summary of the vibrissal sensory system of the rat. The orderly arrangement of whiskers on the rat snout (rows A, B, C, D, E and arcs 1, 2, etc.) is represented centrally by arrays of cellular aggregates in the brainstem (PR5 and SP5I), thalamus (VPm and Po) and somatosensory cortex (S1). The upper left hand frame shows the layout of cortical barrels in an oblique frontal section passing through the second arc of barrels (dashed line drawn through the tangential representation of the barrel field in the upper right hand frame). Abbreviations: SP5O (spinal trigeminal nucleus pars oralis), SP5C (spinal trigeminal nucleus pars caudalis) and S2 (second somatosensory area). See text for a more complete description and for the meaning of the other abbreviations. Part of the schema was modified by Durham and Woolsey [28].

injection of a single cortical barrel [56], there is good reason to believe that the labeling resulted from tracer uptake by damaged fibers de passage. Indeed, it is not uncommon to observe axonal branches of VPm axons coursing tangentially toward their target barrel in layer 4 or in the infragranular layers after the solid labeling of



VPm axons with anterograde tracers. In addition, the staining of single VPm fibers either with the Golgi impregnation or with axonal tracers never provided evidence of a multibarrel innervation by these axons [11,44,63,118].

4.2. Projections from the posterior group

The medial part of Po (Pom) gives rise to a second thalamic projection to S1. This projection arises from cells scattered throughout the rostrocaudal extent of the nucleus [30] and innervates both the granular and dysgranular fields of S1. When the distribution of thalamic afferents to S1 was examined in tangential sections cut through layer 4, complementarity patterns of VPm and Po projections were reported, leaving the impression that Po axons terminate exclusively in the dysgranular zone and interbarrel septa [54]. Although both projections do form spatially segregated terminal fields in layers 3–4, the other layers within the barrel columns are not devoid of Pom input. Yet, the laminar distributions of these two projections remain largely segregated. While VPm terminals are found in layers 6 and 3–4 in the barrel area, Pom terminals are distributed from upper layer 5 to layer 1 of the dysgranular zone, as well as in layers 5 and 1 of the barrel area [40,64]. Thus, the dysgranular zone receives input exclusively from Pom, whereas the barrel columns receives inputs from both Pom and VPm.

The labeling of single axons issued from different parts of Po reveals a heterogeneous population of fibers which, collectively, project across all the somatomotor regions of the neocortex: S1, the second somatosensory, perirhinal, insular and motor cortices. The great majority of these axons ($>80\%$) divide in the white matter at their exit from the striatum and send branches in different cortical areas. The laminar distribution of terminal fields varies across areas, but layers 5a and 1 are usually the most densely innervated. Figs. 3 and 4 illustrate different projection patterns of single Pom neurons. It should be noted that cells labeled at the same injection site in Pom generally project to the same cortical regions. Thus, the Po nucleus appears as a collection of discrete neuronal assemblies that have in common a multiareal projection pattern.

4.3. Projections from the intralaminar nuclei

The intralaminar nuclei have long been considered as the rostral continuation of a nonspecific arousing system taking origin in the dorsal mesencephalon. These nuclei receive indeed a heavy innervation from the cholinergic groups of the brainstem [39,111], but their cortical projections, as reported in all studies using modern tract tracing techniques, are far more specific than what was previously suspected. Their preferential distribution in the mid-cortical layers of the motor areas and deep layers of the sensory specific regions dismisses the long standing concept that intralaminar nuclei give rise to nonspecific thalamocortical projections that terminate in layer 1 over large expanses of the neocortex [10,36,40].

A fair number of intralaminar neurons can be retrogradely labeled when tracers are injected in the deep layers of the rat S1 area [30,76,118]. These projections arise from the CL, Pc and CeM nuclei which provide sparse, but widespread innervation to the deep layers of both the granular and dysgranular zones [10,40]. The selective arborization of intralaminar axons in layers 5 and 6 of the rat S1 area was recently confirmed at a single cell level [118] (see Fig. 5). This study further showed that the intralaminar projection to S1 arises from branching axons whose main termination sites are the layers 3 and 5 of the frontal motor areas.

5. Corticothalamic projection systems

In rats, as in all mammals, CT projections arise exclusively from the pyramidal cells of layers 5 and 6. Though the number of CT cells residing in layer 6 seems particularly high, it has been shown that these are independent of other layer 6 cells projecting to the claustrum or to other cortical areas [48,60,117]. Many studies have now reported that, in sensory specific cortical areas, there is a laminar segregation of the CT cells that project to different thalamic nuclei [14,15,17,22,34,35,103]. It is not yet known whether a similar segregation exists in the parasensory and motor cortical fields. Present evidence clearly indicate, however, that in the primary sensory areas, the position of a CT cell within a cortical column relates to its projection target(s) in the thalamus.

5.1. Two types of corticothalamic fibers

On the basis of the intrathalamic distribution of axonal fields and of the morphology of terminations, two types of CT fibers were seen to arise from the visual, somatosensory, auditory and motor cortices in mice, rats, cats and monkeys [14,15,37,42,61,79,86–88].

The first type, which arises from layer 5 cells, is a collateral projection issued from long-range axons that project to the brainstem and/or the spinal cord. These axons do not supply branch to the thalamic reticular nucleus nor to the sensory-specific thalamus, but to intralaminar and association nuclei in which they form small clusters of large terminals (3–8 μm). At the ultrastructural level, terminals form glomerular synapses with the proximal dendrites of relay neurons [42,79,88]. The fine-grained distribution of layer 5 afferents in the thalamus is not well known. For the moment, it would be premature to comment on the reciprocity of these connections. Interested readers should consult the recent review of Sherman and Guillery [93] and the discussion in Diamond et al. [26] for additional information.

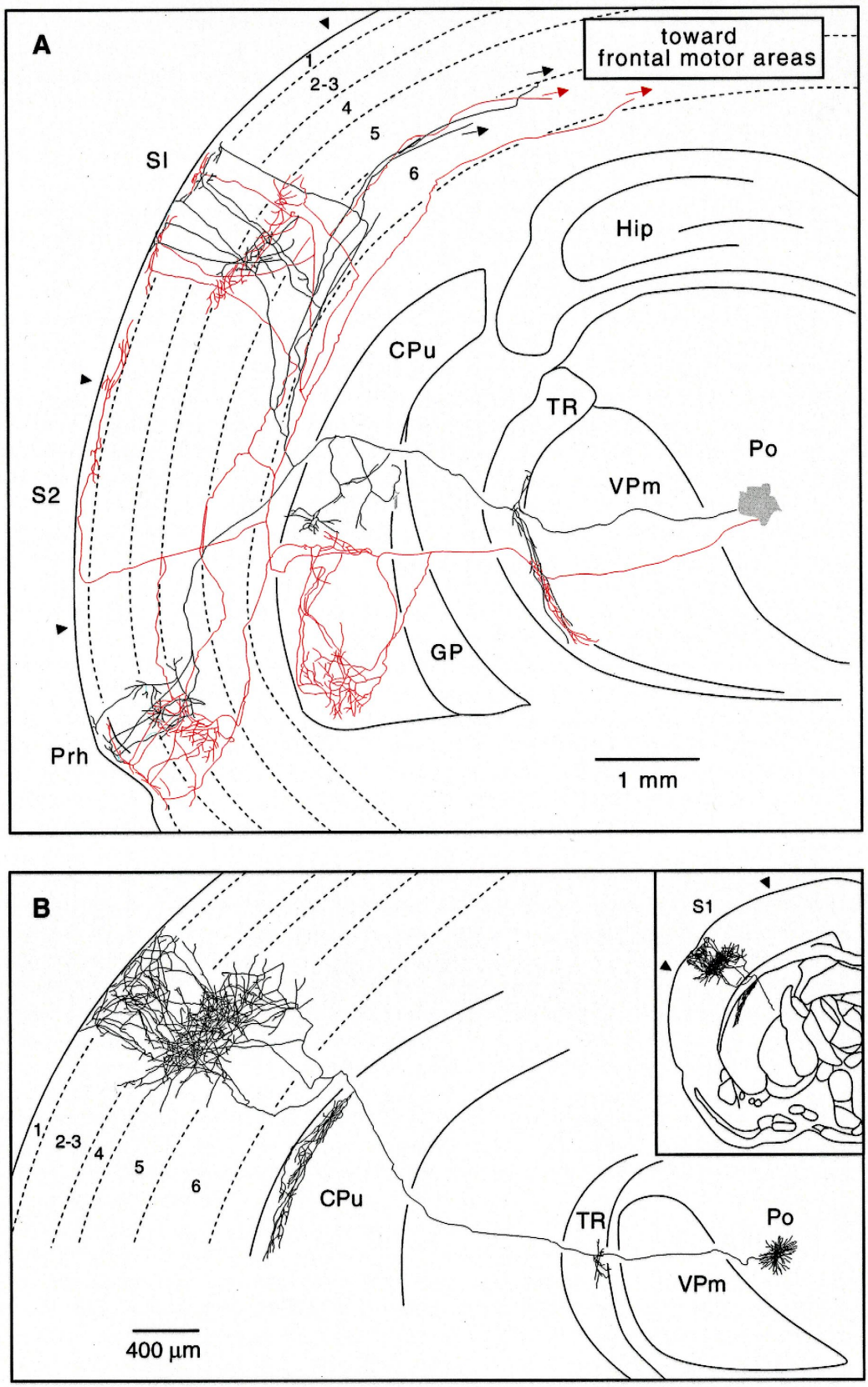


Fig. 3. Camera lucida reconstructions of the axonal projection of three Po neurons. Fibers in A were labeled by a small extracellular injection of BDA and cell in B was labeled juxtacellularly. Abbreviations: CPu (caudate–putamen), GP (globus pallidus), Hip (hippocampus), Prh (perirhinal cortex), S2 (second somatosensory cortex) and TR (thalamic reticular nucleus). See text for the other abbreviations.

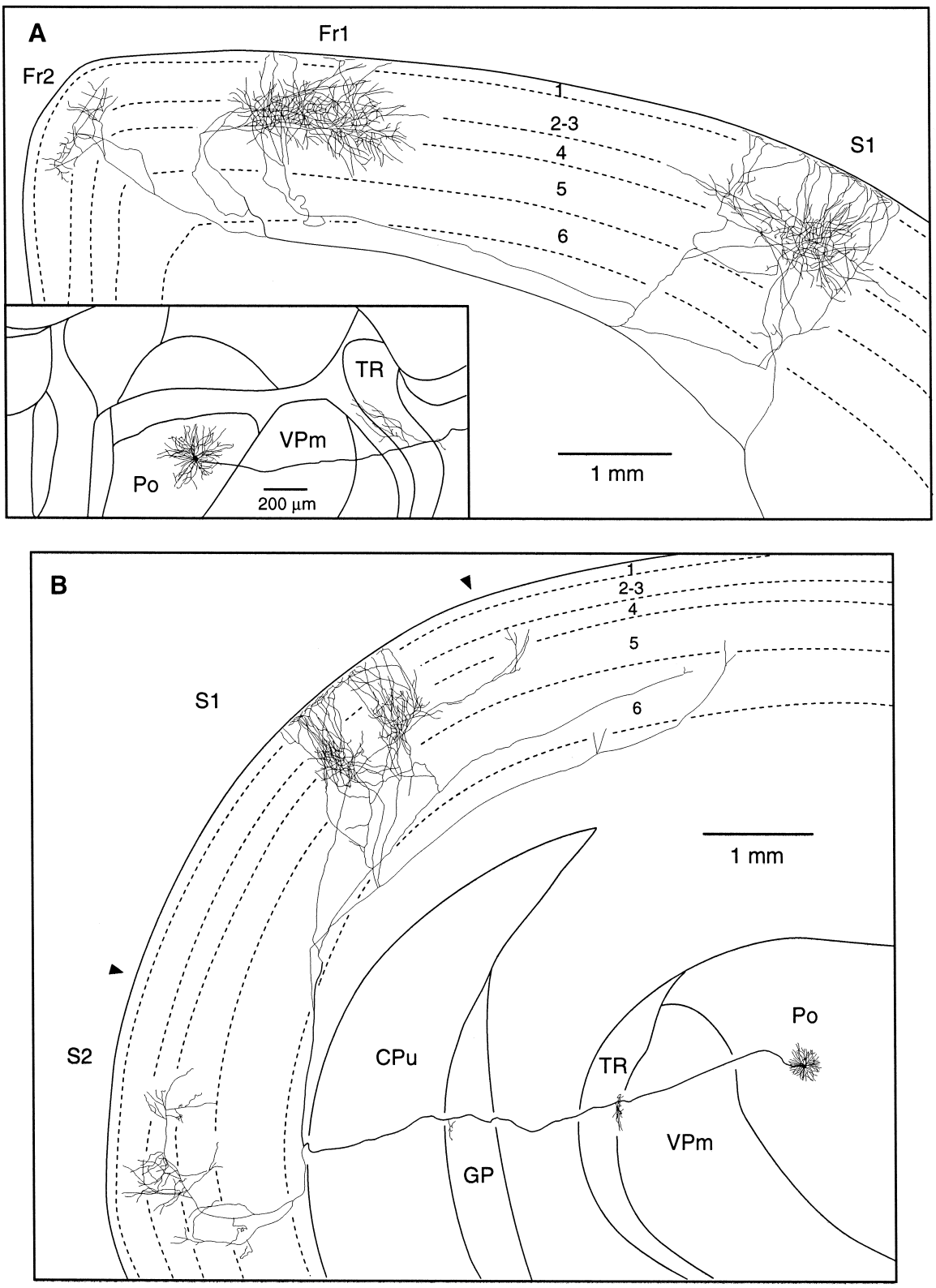


Fig. 4. Camera lucida reconstructions of the axonal projection of two Po neurons. Both cells were labeled by juxtacellular applications of BDA. Note that in A, the terminal fields in Fr1 and S1 were located on different frontal planes about 4 mm apart. Insert shows the location of the relay cell in Po. Abbreviations: CPu (caudate–putamen), Fr1 (frontal cortex area 1), Fr2 (frontal cortex area 2), GP (globus pallidus), S2 (second somatosensory cortex) and TR (thalamic reticular nucleus). See text for the other abbreviations.

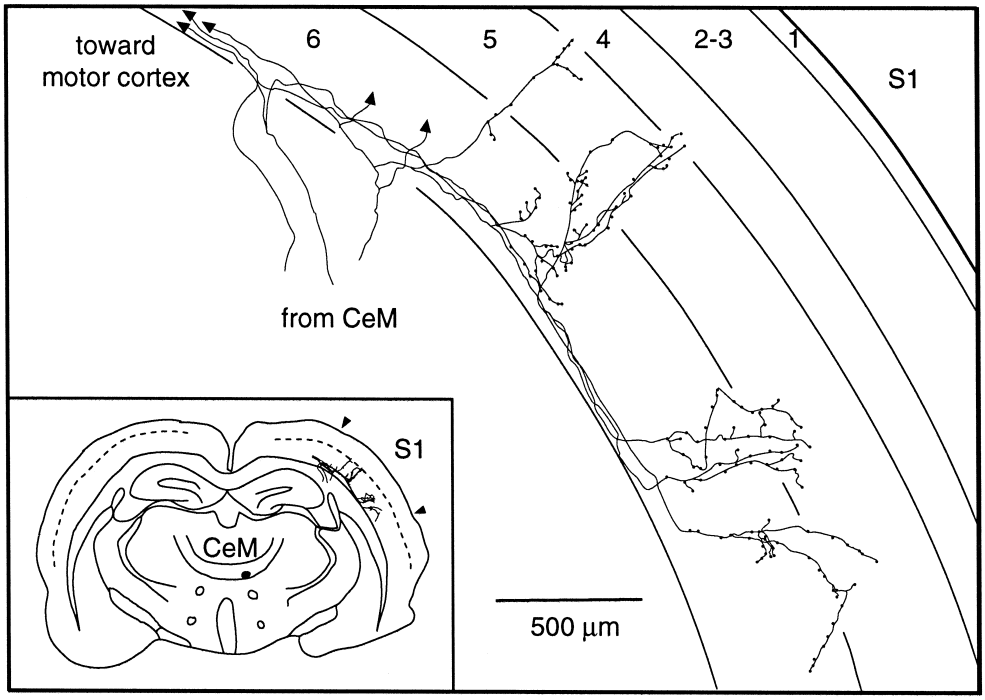


Fig. 5. Camera lucida reconstruction of the arborization of three CeM axons projecting to the rat somatosensory cortex. Insert shows the location of the axonal arbors and injection site on a frontal section. The dashed line indicates the lower limit of layer 4. Note that the projection to S1 arises from branches of parent axons reaching the frontal motor areas.

The second type of fibers, which are the most numerous, arise from layer 6 cells, supply axon collaterals to the reticular nucleus and distribute branches bearing arrays of small drumstick-like terminations (≈ 1 μm) across most of the thalamic nuclei. These CT terminals are presynaptic to the distal dendrites of thalamic relay cells [46,62,66,96]. Whether these fibers establish reciprocal patterns of connections is the central issue of the present review.

5.2. Layer 6 corticothalamic cells

The anterograde labeling of small aggregates of CT cells at different depths in layer 6 of the primary sensory areas in rat revealed a diversity of terminal arbors in the thalamus [14,15]. The upper part of layer 6 contains cells that project exclusively to the sensory specific nuclei (the dorsal lateral geniculate nucleus or the ventrobasal nucleus), where they form barrel-like or rod-like terminal fields (Fig. 6A). Those located deeper in layer 6 generally exhibit a multinuclear innervation pattern. They innervate large sectors of the associative and/or intralaminar thalamic territories that are affiliated with each of these sensory modalities (the lateral dorsal–lateral posterior nuclei or the posterior group) and also participate in the formation of rods or barreloids in the specific nuclei. Similar lamina-dependent differences in the distribution of CT projections have been reported in the auditory system of the cat [79] and in the visual system of the tree shrew [103]. It is not yet known, however, whether the CT cells in higher order cortical areas are segregated in layer 6 according to their thalamic projections.

5.3. Corticothalamic projections from the barrel field

Only two studies have investigated the topographical relationships between single cortical barrels and thalamic barreloids. The first, carried out in mice, and the second in rats, arrived at almost opposite conclusions. Following *Phaseolus vulgaris*-leucoagglutinin (PHA-L) and horseradish peroxidase (HRP) injections restricted to a single barrel column in the mouse, Hoogland et al. [41] reported that CT fibers formed rostrocaudally oriented bands in VPm, distributing terminals across a series of barreloids representing together an arc of vibrissae. Retrogradely labeled cells, however, were found in a unique aggregate that outlined the shape of a single barreloid. Thus, while the feedforward thalamocortical pathway implies a one-to-one correspondence between thalamic barreloids and cortical barrels, the feedback CT pathway distributes more extensively in a manner inconsistent with a rule of strict reciprocity. A very different conclusion was reached by Land et al. [56] who partly re-examined this issue in the rat. By using HRP to map connections both anterogradely and retrogradely, these authors concluded that the thalamocortical and CT connections in the rat vibrissa–barrel system were highly reciprocal and that species differences

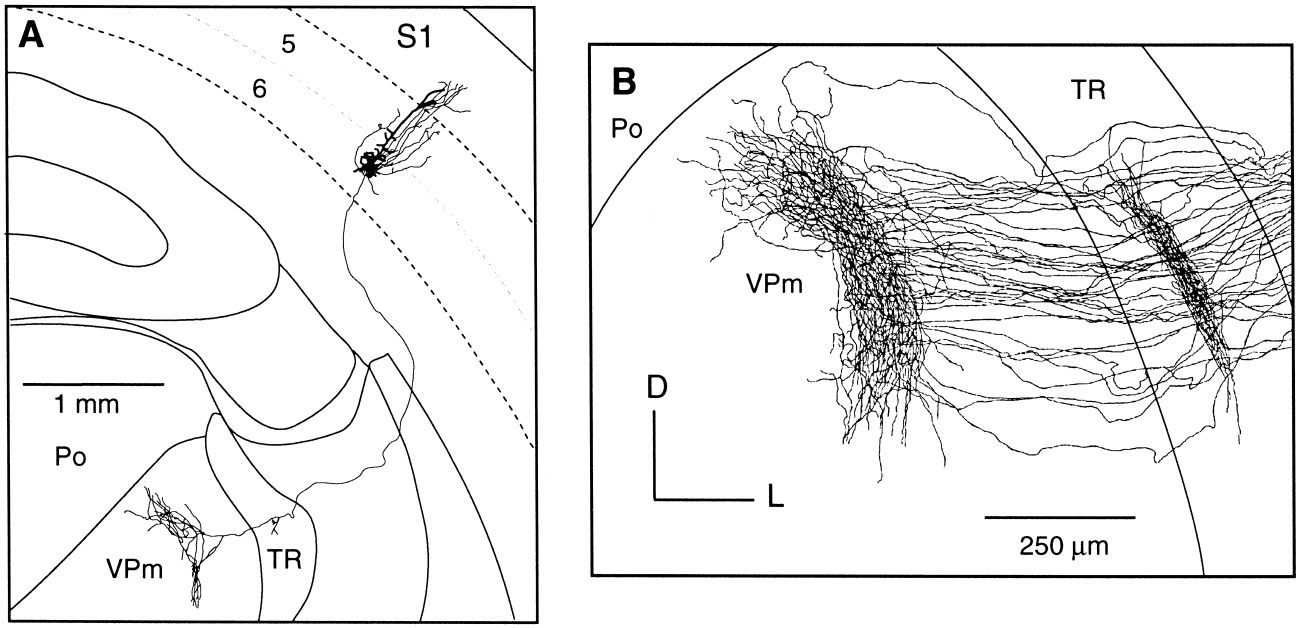
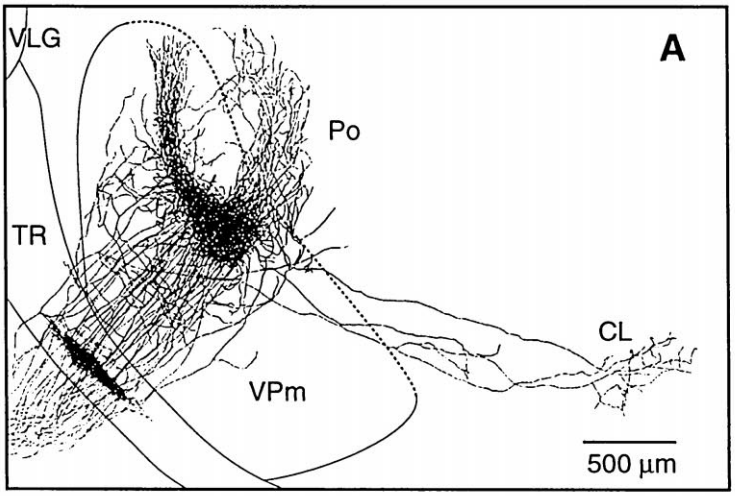


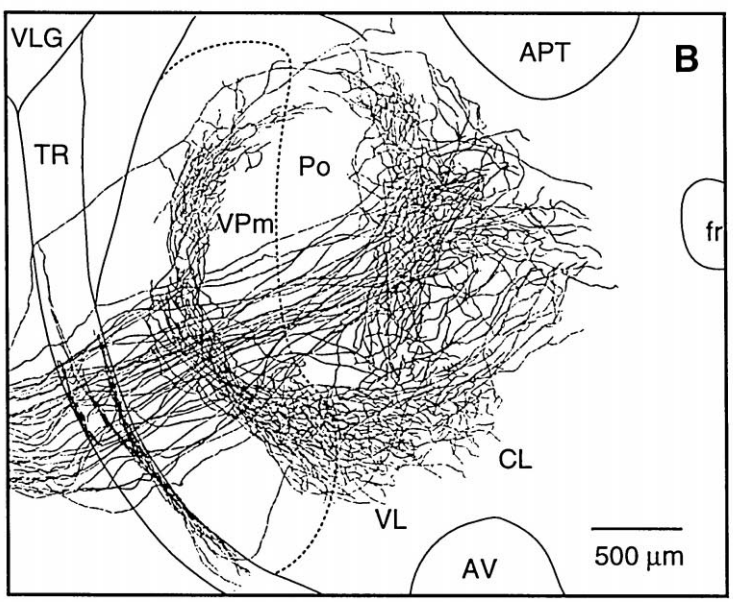
Fig. 6. Camera lucida reconstructions of the CT projections arising from the upper part of layer 6 in the rat barrel cortex. The cell in A was injected juxtacellularly with biocytin. The CT fibers shown in B were labeled after a small BDA injection made in the upper part of layer 6 beneath barrel B3 (depth = 1500 μm). Abbreviation: TR (thalamic reticular nucleus).

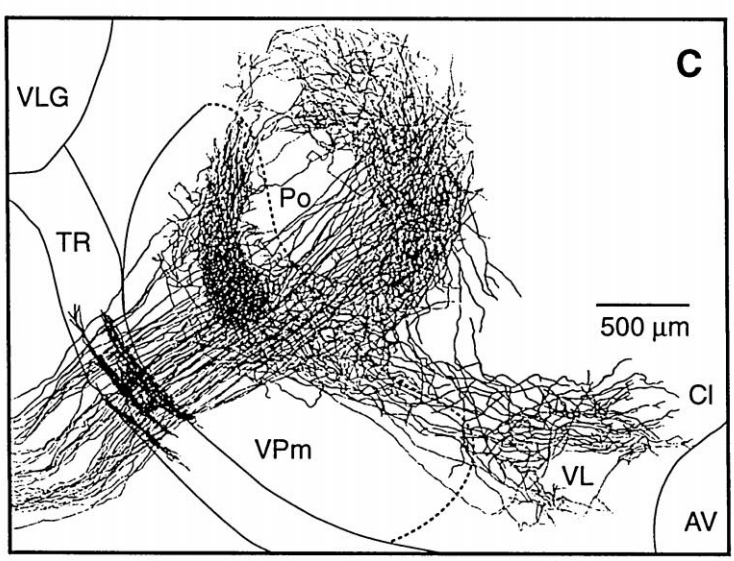
might be at the origin of the discrepancy. Notwithstanding the fact that HRP is less sensitive than PHA-L to trace anterograde connections, a close look at the injection sites illustrated in Land et al.'s paper (see Fig. 5 in Ref. [56]) reveals that tracer deposits were almost completely restricted to the upper half of layer 6 of a barrel column. We recently re-examined the topography of the CT projections of physiologically identified barrel columns in rats by injecting biotinylated dextran amine (BDA) at different depths in layer 6 and by labeling also the full extent of layer 6 with a roving micropipette. Following small injections of BDA in the upper part of layer 6 (depth = 1500 μm), the terminal labeling in VPM is restricted to a small territory resembling in dimension and orientation to the cytochrome oxidase-rich barreloid described by Land et al. [56]. Fig. 6B shows such a case where all CT axons converge on the same termination site in VPm. After slightly bigger injections centered in the upper part of layer 6, labeled fibers form a compact, sharply defined plexus in VPm which is accompanied by sparse labeling in Po and CL nuclei (Fig. 7A,D). Serial reconstruction from horizontal sections reveals the barreloid-shaped terminal field in VPm. In contrast, when injections of similar size are made in the lower part of layer 6 (depth = 1800 μm), a barreloid-like terminal field is hardly discernible in VPm. Instead, CT fibers are seen to invade Po and form a rostrocaudally oriented band in the dorsal part of VPm (Fig. 7B). Injections that span across the full depth of layer 6 result in a composite terminal field made of the two preceding projection patterns (Fig. 7C). In VPm, the topographical arrangement is such that the whole projection of a single barrel column forms an orthogonal array of terminations across the field of barreloids.

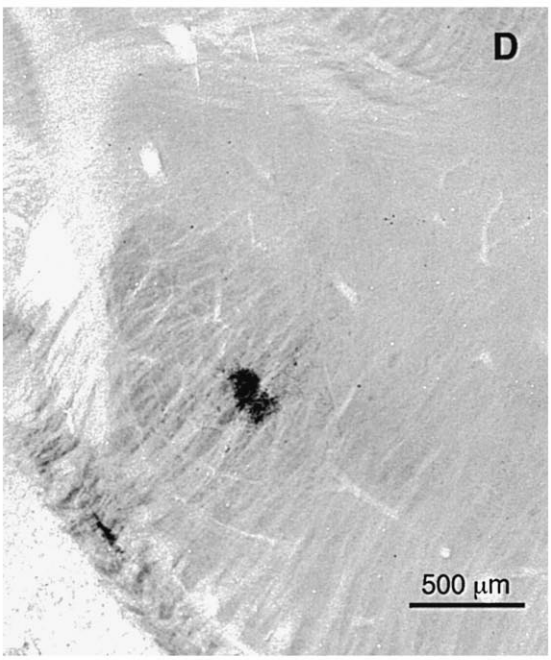
Using the same material, we examined in detail the branching pattern of single fibers that coursed at the periphery of the darkly stained terminal field in VPm. These axons, which likely arise from the lower half of layer 6, exhibit a great diversity of branching patterns (Fig. 8). Most axons branch to the barreloid corresponding to their barrel of origin, but they also project to adjacent regions of VPm, particularly to the dorsal fringe of the nucleus abuting Po, to Po and/or the intralaminar nuclei. A few also send branches to the ventral lateral nucleus, the medial division of the medial geniculate body or to VM.

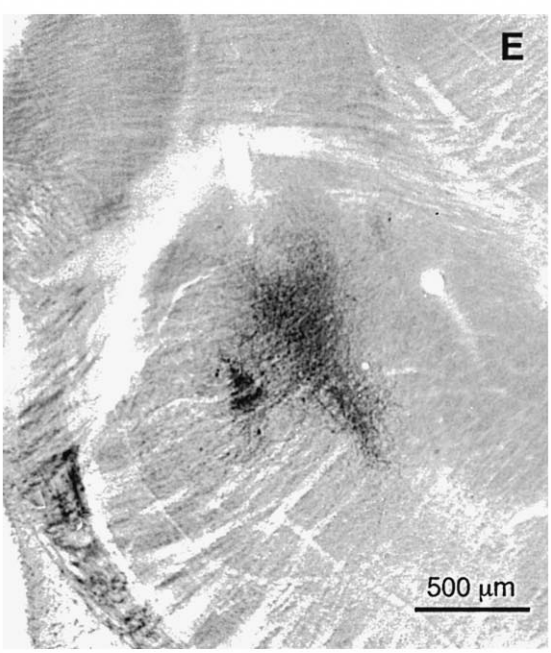
Fig. 7. Reconstructions from serial horizontal sections of the CT projections issued from the rat barrel field. Drawings A, B and C show terminal fields labeled after the injections made in the upper part of layer 6 (depth = 1550 μm) of the barrel column D4 (A), in the lower part of layer 6 (depth = 1800 μm) of the barrel column E2 (B) and across the full extent of layer 6 of the barrel column C4, respectively. Photomicrograph D shows the dense punctate appearance of the CT terminal field in VPm after an injection made in the upper part of layer 6; note the short narrow band of terminals in the central tier of the thalamic reticular nucleus. Photomicrograph E shows labeling in VPm and Po after an injection made across the full extent of layer 6. Note also the presence of two bands in the central and inner tiers of the thalamic reticular nucleus. Both photomicrographs were taken from horizontal sections. Abbreviations: APT (anterior pretectal nucleus), AV (anterior ventral nucleus), fr (fasciculus retroflexus), TR (thalamic reticular nucleus), VL (ventral lateral nucleus) and VLG (ventral lateral geniculate nucleus).


A
VLG
Po
TR
CL
VPm
500 µm


B
VLG
APT
TR
Po
VPm
fr
CL
VL
AV
500 µm


C
VLG
Po
TR
500 µm
Cl
VPm
VL
AV


D
500 µm


E
500 µm

5.4. Corticothalamic projections from the dysgranular zone

Sparse anatomical data exist concerning the CT projections issued from the dysgranular zone of S1 in the rat. We know of only one study that examined in detail the precise location of CT cells within the barrel field following small injections of a tracer into the physiologically defined whisker representation in VPm [21]. This study reported that retrogradely labeled cell bodies were distributed over a broader expanse of the cortex than the anterograde labeling used to define barrel columns. In tangential sections, a fair proportion of CT cells were found in layer 6, deep to the septal regions. We recently addressed this question by labeling anterogradely small pools of CT cells within the broader dysgranular region that surrounds the barrel field. Injections in layer 6 of the cytochrome oxidase-poor dysgranular zone consistently label fibers that project to both VPm and Po (Fig. 9). In contrast with the laminar segregation of the CT populations observed in the barrel columns, CT cells of the dysgranular zone with a dual thalamic projection are located throughout the full depth of layer 6.

5.5. Bilateral corticothalamic projections

In a number of species, many studies have now convincingly demonstrated that some cortical areas give rise to bilateral CT projections. Such projections are not only present in midline nuclei, where one could suspect an irregularity of the position of the midline, but also in many nuclei situated at a distance. In rats, bilateral CT projections have been reported in nuclei of the anterior group from the cingular, retrosplenial and presubicular areas [47,78] and in the medial dorsal and submedial nuclei from the medial and orbitofrontal regions [8,59,85]. The best documented case concerns the CT projections from the motor and premotor frontal areas [73]. After injection of WGA–HRP in the rat motor cortex, terminal labeling was reported present bilaterally in the ventral lateral, ventral medial and posterior group nuclei, but more importantly in the anterior and posterior intralaminar nuclei. These bilateral CT projections arise from branching axons as revealed by the anterograde labeling of small groups of cells in the deep layers of the rat motor cortex. Both layer 5 and 6 cells contribute to the contralateral projections with a more important contribution from the latter. Fig. 10 shows the reconstruction of the axonal arborizations of two bilaterally projecting neurons.

6. Summing-up

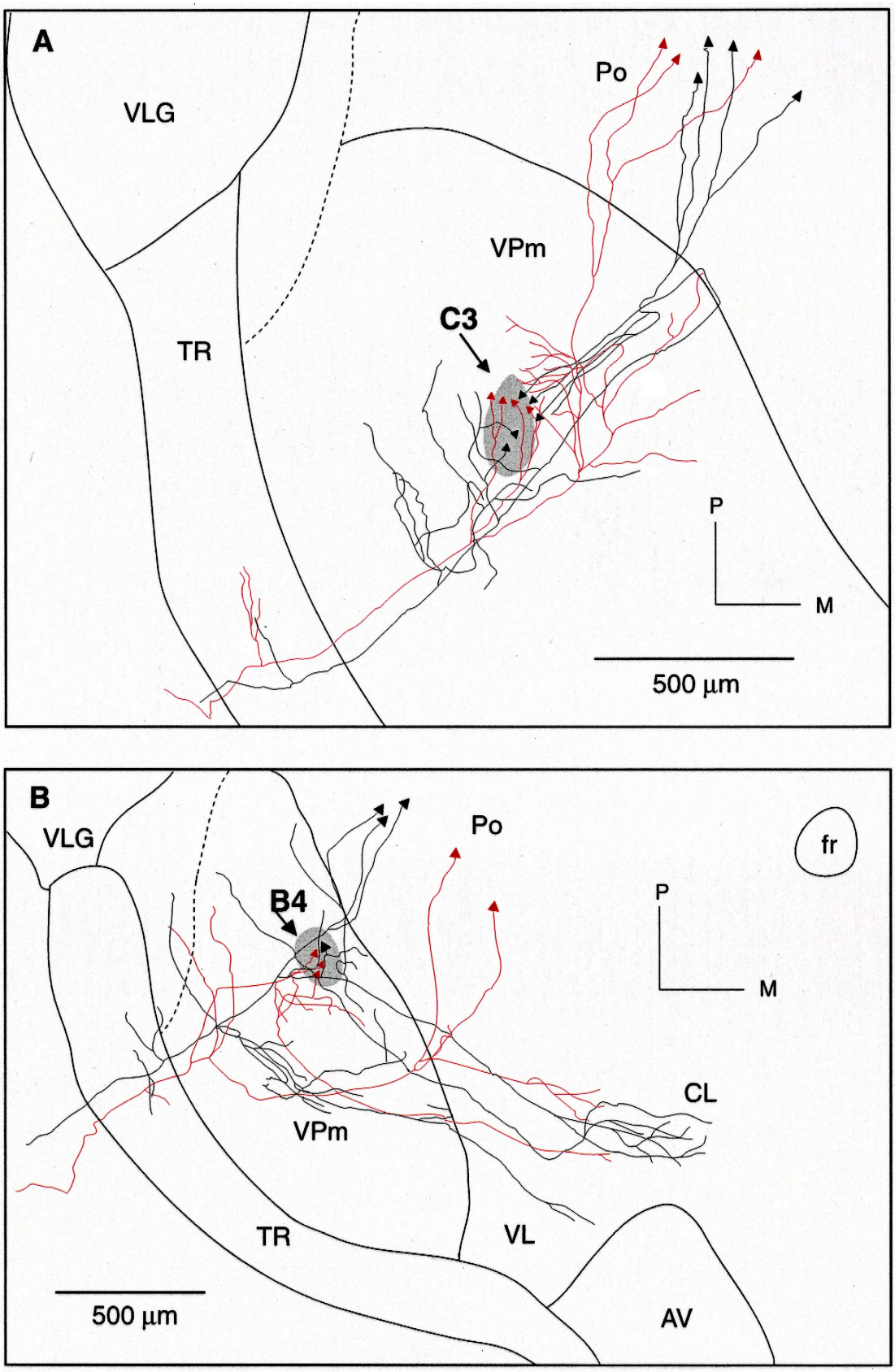
In the preceding sections, we presented anatomical data which, albeit restricted in scope, illustrate some inconsistencies between the principle of reciprocity and the actual organization of CT connections. These data show that, in the rat somatosensory cortex, (1) CT cells in the upper part of layer 6 of a barrel column establish a one to one reciprocal relationship with the corresponding thalamic barreloid; (2) CT cells in the lower part of layer 6 not only reciprocate the other thalamocortical projections received by the barrel column, but they also innervate in a nonreciprocal manner other barreloids within VPm; (3) the dysgranular zone of S1 which does not receive afferents from VPm, projects to VPm; and (4) finally, many cortical areas project bilaterally in the thalamus although none of these projections were shown to be matched by bilateral thalamocortical projections. Points (2), (3) and (4) represent major infringements of the principle of reciprocity, and most neuroanatomists will admit that these infringements fall short of a more comprehensive explanation. Here, we shall propose that the spatial organization of CT connections complies with a more fundamental rule, the rule of parity, from which reciprocity follows as a general, but not obligatory consequence.

7. The rule of parity

The rule of parity states that the topographical distribution of CT projections is determined by the branching patterns of the different classes of prethalamic afferents (see Fig. 11). Thus, if nucleus X receives a type 1 prethalamic input and projects to area A, then area A returns a type 1-like projection to nucleus X. If nucleus X receives a type 2 prethalamic input and projects to area A, then, area A returns a type 2-like projection to nucleus X. If nucleus X receives both type 1 and type 2 prethalamic inputs and projects to area A, then, area A gives rise to two types of CT fibers that match both sets of prethalamic inputs. In the visual and vibrissal somatosensory systems, type 1 and type 2 afferents may correspond, for instance, to units that respond either phasically or tonically to sensory stimulation.

Four aspects of this rule need precision. First, the pairing of CT and prethalamic projections occurs only between fibers of like functional classes, which implies that there are categories of CT fibers corresponding to

Fig. 8. Partial reconstructions of single CT axons labeled following BDA injections made in layer 6 beneath the physiologically identified barrels C3 (A) and B4 (B). Grey areas indicate the location of the densely stained corresponding barreloids in VPm. During the injection, the micropipette was moved up and down between depths of 1550 and 1900 μm in steps of 10 μm every 10 s; total injection time = 1 h, survival period = three days. Drawings were made from serial horizontal sections. Abbreviations: AV (anterior ventral nucleus), fr (fasciculus retroflexus), VL (ventral lateral nucleus), VLG (ventral lateral geniculate nucleus) and TR (thalamic reticular nucleus).


A
VLG
Po
VPm
C3
TR
P
M
500 µm
B
VLG
Po
fr
B4
P
M
CL
VPm
TR
VL
500 µm
AV

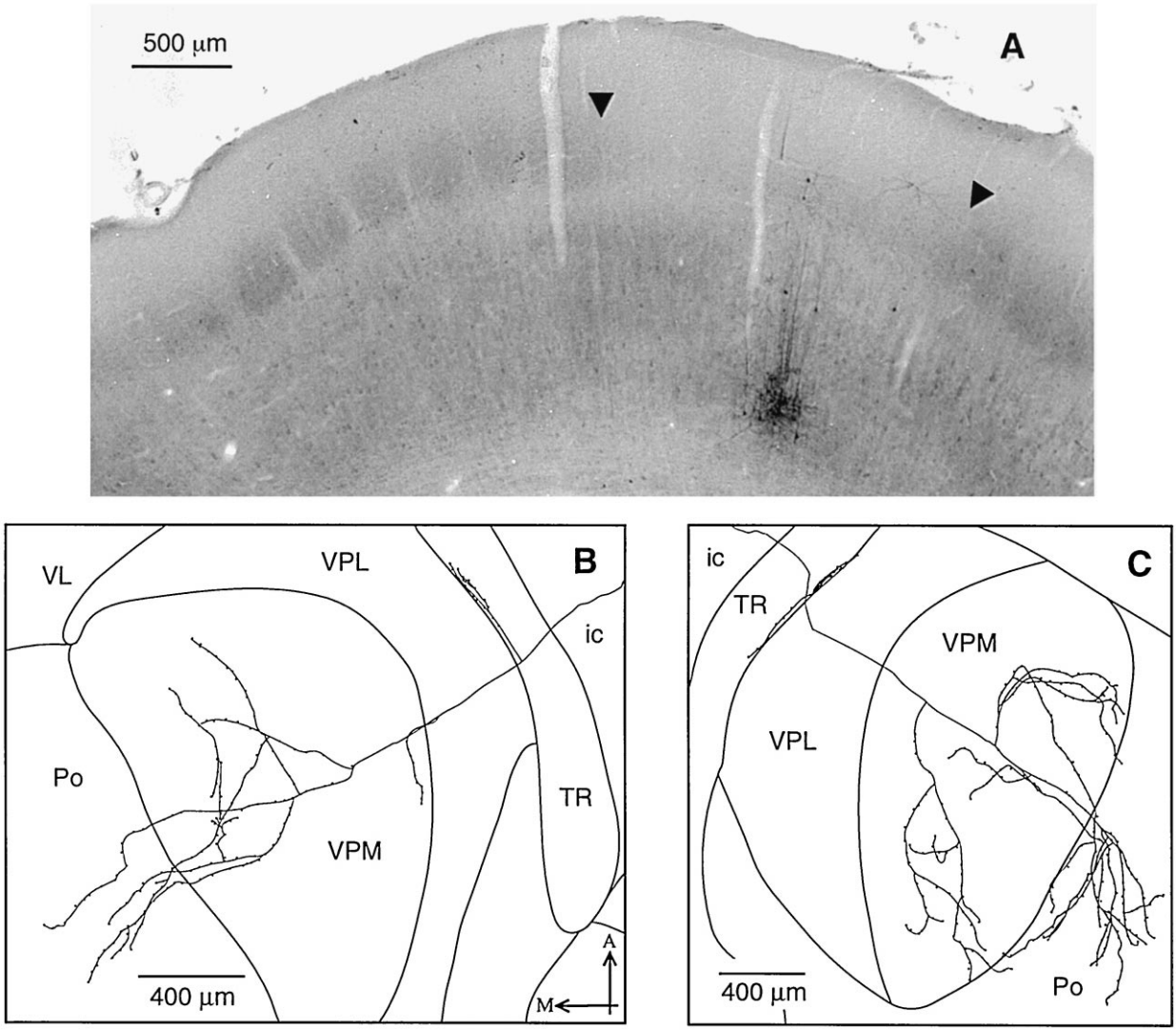


Fig. 9. Axonal projections of single CT fibers from the dysgranular zone of S1 in the rat. Photomicrograph A shows an injection site in the cytochrome oxidase poor region of S1 (region between the arrowheads); the tissue was cut along an oblique frontal plane to better visualize the barrels. Fibers in B and C were labeled after injections made in the lower and upper parts of layer 6, respectively. Fiber reconstructions were made from horizontal sections.

those present in prethalamic pathways. Secondly, pairing does not mean that the terminal arbors of CT cells form mirror copies of their prethalamic counterparts. If a relay cell is contacted by three prethalamic fibers of the same class whose receptive fields overlap, the projection returned by the cortex to this relay cell may exhibit, at a single cell level, a spatial distribution corresponding to the weighted average of the three prethalamic fibers. These topographical singularities will be masked after the labeling of a large number of like cells in the cortex. Thirdly, since parity is an operational rule, its implementation implies 'hand-shaking' molecular mechanisms through which paired connections are established during development. This issue will be discussed in Section 7.4. As a final specification, it should be mentioned that the rule of parity applies only to the glutamatergic prethalamic inputs as there is no reason to believe that GABAergic, aminergic or cholinergic systems, which exert primarily a modulatory function, are matched by corresponding CT pathways.

As a necessary consequence, the rule of parity will generate much reciprocal connections between the thalamus and cortex, but cases of nonreciprocity are not excluded. Such a situation is depicted in the diagram of Fig. 12. Let's suppose that a sensory system comprises two types of prethalamic fibers. Type 1 fibers, which contact exclusively a small pool of relay cells within the sensory specific nucleus X, and type 2 fibers, which bifurcate to contact the same pool of relay cells in nucleus X, as well as other cells in the associative nucleus Y. Relay cells in nucleus X then establish a point to point relationship with the primary sensory cortical area A, whereas the relay cells of nucleus Y project to both cortical areas A and B. According to the rule of parity, cortical area A will give rise to two types of CT fibers that will match the arboriza-

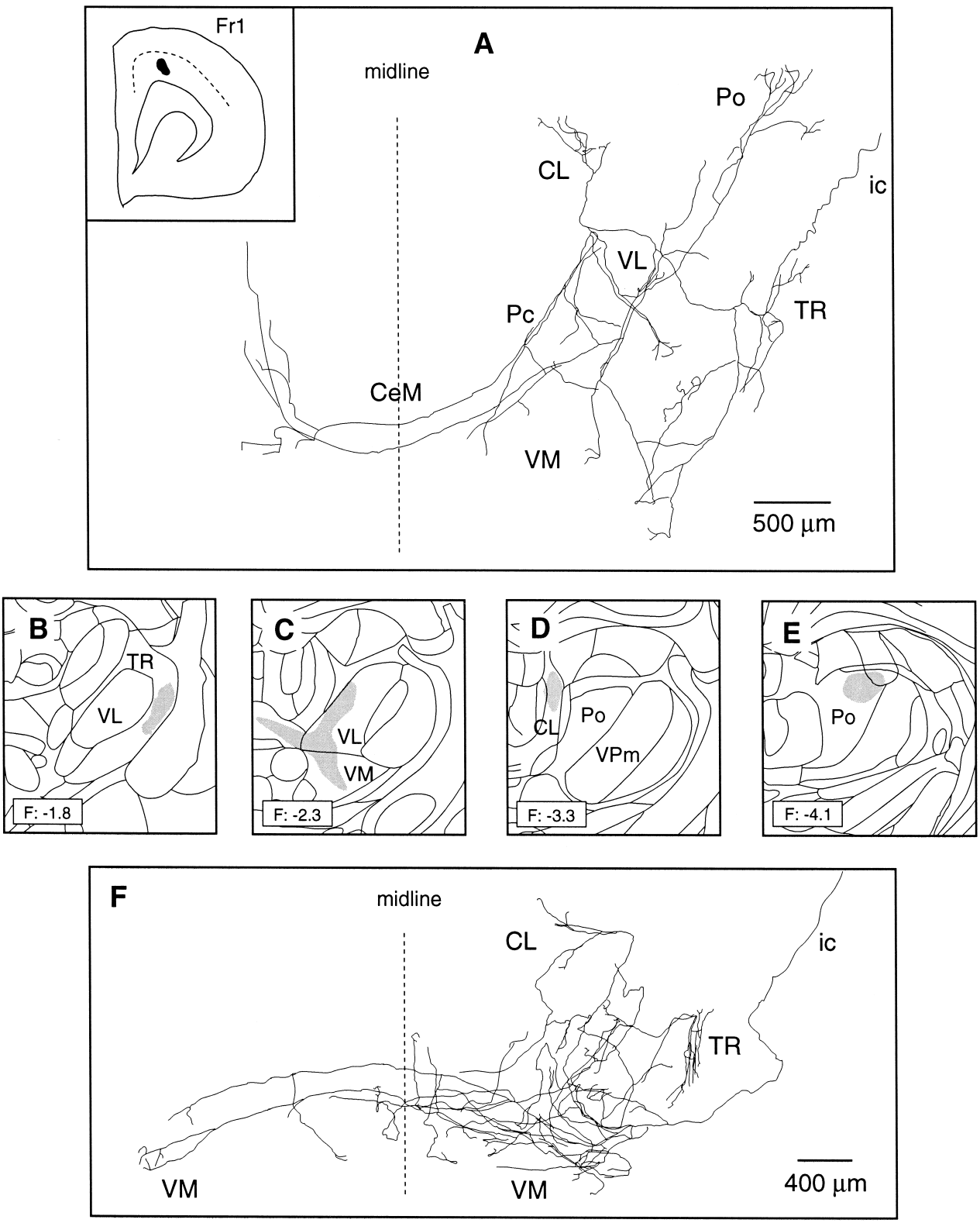


Fig. 10. Camera lucida drawings showing bilateral projections of single CT fibers from the rat vibrissal motor cortex. The multinuclear distribution of the CT axon in A is shown across a series of frontal sections in B–E. Frontal planes refer to distances from the bregma according to the atlas of Paxinos and Watson [80]. Insert in A: site of BDA injection in the motor cortex (Fr1: frontal cortex, area 1); the dashed line indicates the upper limit of layer 5. Drawing in F illustrates a CT fiber that innervates principally the ventral medial nucleus.

tion patterns of both types of prethalamic inputs, while area B will give rise to a single type of CT fibers that will project to both thalamic nuclei. Within this scheme, most of the CT projections will reciprocate the thalamocortical inputs, except those from area B to nucleus X. This is actually the type of organization that seems to prevail in the vibrissal sensory system of the rat. Although relevant information is still scanty concerning the fine organization of other CT pathways, available evidence indicates that the rule of parity might also apply to other sensory systems. In the auditory system of the cat, Diamond et al. already noticed that ‘‘...the corticogeniculate fibers vary in size and terminal pattern in a manner closely related to those shown by the ascending afferents to these nuclei’’ [27], and in the cat visual system, there is an evidence that the terminal fields of single CT axons in the dorsal geniculate nucleus are at least as diversified as those of the various classes of retinal afferents [16,74,98–100]; see Section 7.5.

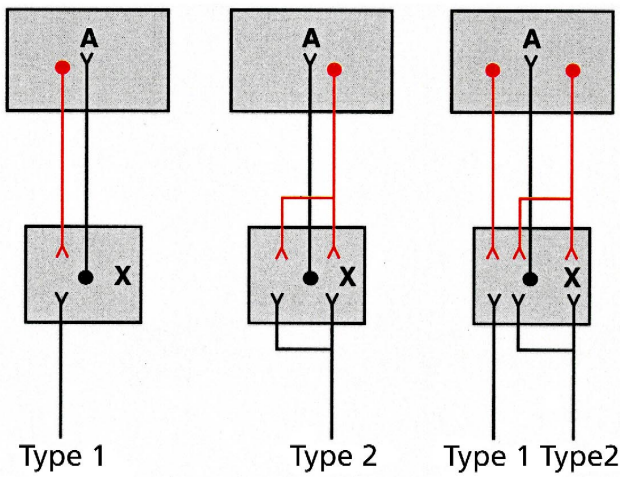


Fig. 11

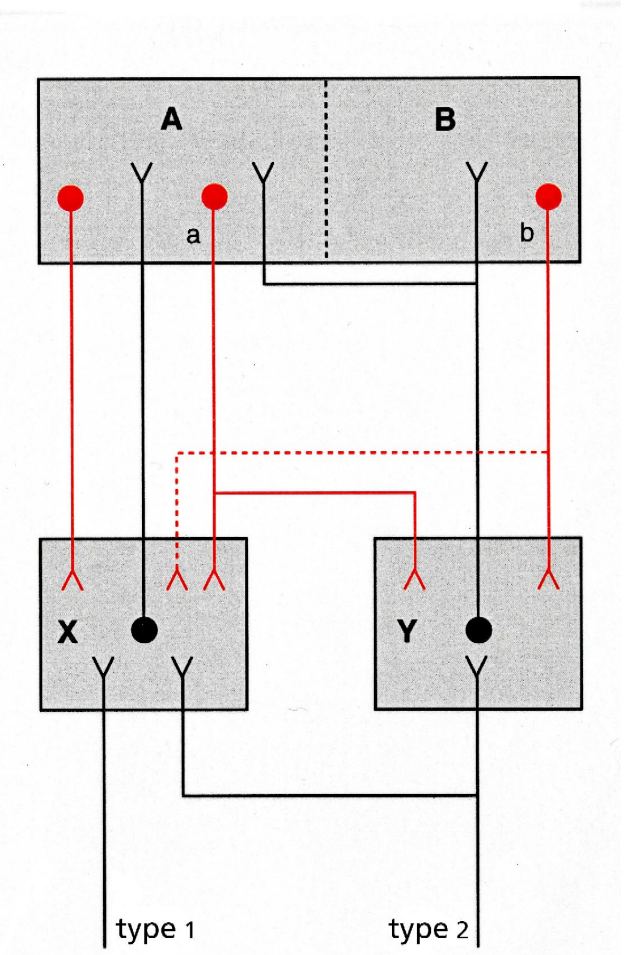


Fig. 12

7.1. Parity in the vibrissal sensory system of the rat

The correspondence between the arrangement of descending and ascending pathways in the rat somatosensory thalamus offers a striking illustration of the rule of parity. Like the CT projections arising from the upper and lower parts of layer 6, the Pr5 and Sp5I inputs have largely complementary projection patterns in the thalamus. Both, upper layer 6 cells in a barrel column and Pr5 neurons in a brainstem barrelette establish a one-to-one relationship with their corresponding barreloid in VPm. Likewise, CT cells of the lower part of layer 6 and SP5I afferents form mirror-image terminal fields in VPm, Po and intralaminar nuclei (compare Figs. 1 and 2 in Williams et al. [108] with Fig. 7 of the present review). Although striking, these correspondences remain gross for the moment, and the way these matching topographical patterns are generated at a single cell level remains to be established.

There exists little information concerning the axonal arborization of physiologically characterized trigeminothalamic cells. Intra-axonal labeling of a few vibrissa-driven Pr5 fibers at their entry in the thalamus revealed terminal arbors that are spatially restricted to the size of a barreloid [108]. This is likely the case of the thicker axons, because bulk anterograde labeling studies also revealed a Pr5 projection to Po. No information is presently available concerning the terminal arbor of single Sp5I axons in the rat thalamus. As a whole, the Sp5I has robust projections to nonbarreloid thalamic regions, including the Po, the intralaminar nuclei, the dorsal fringe of VPm covering the barreloids and the interbarreloid septa [29,108]. Intracellu-

Fig. 11. Schematic illustration of the rule of parity. Corticothalamic projections from cortical area A to nucleus X match the different classes of prethalamic afferents that influence area A via nucleus X. Full description in the text.

Fig. 12. Schema showing how the rule of parity allows reciprocal, as well as nonreciprocal connections between thalamic nuclei (boxes X and Y) and cortical areas (boxes A and B). The dashed line represents a case of nonreciprocity. See text for the meaning of cells ‘a’ and ‘b’.

lar recordings and electron microscopic studies have clearly demonstrated, however, that the relay cells within barreloids receive contacts from both the Pr5 and Sp5I afferents [20,105,108].

Given the fact that many CT cells in the depth of a barrel column exhibit a multinuclear innervation pattern, the rule of parity would predict that a fair proportion of trigeminothalamic cells would innervate both VPm and Po by means of branching axons. Admittedly, this prediction goes against the belief that most projections to VPm and Po arise from separate populations of trigeminal neurons [19]. It should be reminded, however, that the retrograde double-labeling technique used to demonstrate these independent populations proved of low reliability in other circumstances to estimate quantitatively the number of branching axons. For instance, it was concluded from this technique that no layer 5 pyramidal cell in the cortex projected to both the thalamus and the brainstem [18], but later studies using anterograde tracers firmly demonstrated that in fact, all layer 5 cells that project to the thalamus also project downstream [24,61]. Thus, it is imperative that the trigeminothalamic projections be re-examined after the anterograde labeling of small groups of axons to determine unequivocally the manner these fibers branch in the thalamus.

On the basis of the patterns of CT projections demonstrated in the rat vibrissal sensory system, the rule of parity predicts the existence of certain CT connections, which otherwise could be considered as unconventional or aberrant. The schema of Fig. 12 can be used to illustrate the situation. Let's suppose that the VPm and intralaminar nuclei are represented by nuclei X and Y, respectively, and that boxes A and B represent S1 and the motor areas, respectively. Anatomical data already showed that the same intralaminar axons project to both area A (S1) and B (motor cortex), and that some CT cells in area A (cell a) project back to both the VPm and intralaminar nuclei. According to the rule of parity, one should find not only prethalamic axons that branch in both the VPm and intralaminar thalamus, but area B (motor area) should also contain some CT cells (cell b) that also innervate the VPm and intralaminar nuclei. At first sight, it seems odd that the motor areas would return axons to the VPm. This prediction was tested by making large BDA injections in the deep layers of the rat vibrissal motor area. At a thalamic level caudal to the ventral lateral nucleus, retrogradely labeled cell bodies and anterogradely labeled CT axons are present in the dorsal part of Po, in the intralaminar thalamus and VM (Fig. 13). The VPm contains no retrograde labeling, but in agreement with the rule of parity, some anterogradely labeled fibers bearing terminations descend from the overlying plexus in Po and terminate in VPm. Admittedly, this projection is sparse, but clearly present. The slenderness of the branches and their departure from Po suggest that they are collaterals of parent axons that innervate either Po or the intralaminar thalamus. The possibility that these axonal branches were filled via the axon collaterals of CT cells in S1 that project to the motor areas appears remote, because no CT cell in the rat S1 was shown to make long range corticocortical connections [117].

7.2. The number of corticothalamic cells

It is one of the most intriguing feature of the thalamocortical relationships that the number of CT cells exceeds by far the population of thalamic relay neurons. In the cat primary visual cortex, their number exceeds the population of thalamocortical cells found in laminae A and A1 of the lateral geniculate nucleus by one order of magnitude [53]. From quantitative studies of other cortical areas [7], a similar figure may also apply to the CT populations projecting to corresponding thalamic nuclei. This large number of CT cells constitutes a fact to which the principle of reciprocity can partly account by postulating much divergence in the projections of thalamocortical systems. Yet, the disproportion between the two cellular populations would require a very large number of thalamocortical branching axons. The rule of parity, however, implies that the number of CT cells within a given cortical area is related to the number of prethalamic afferents that influence this area via the thalamus. The branching diagrams of Fig. 14 illustrate the numerical amplification generated. The principle of reciprocity would require at most two CT neurons (one would suffice!) in cortical area A to reciprocate inputs received from thalamic nuclei X and Y. This yields a ratio of 2:1 between the number of CT cells in area A and the number of relay cells in nucleus X. In comparison, the rule of parity requires a ratio of 4:1 between area A and nucleus X to match the patterns of prethalamic afferents that influence area A via the thalamic nuclei X and Y. Thus, within the parity scheme, the number of CT neurons is commensurate with the degree of divergence and convergence in both the prethalamic and thalamocortical pathways.

7.3. Bilateral corticothalamic projections

Although the output of the thalamus is strictly unilateral (the thalamus of one side projects only to the cortex of the same side), many of its nuclei receive bilateral projections from the cortex. These exceptions to the principle of reciprocity can readily be explained by the rule of parity. All thalamic nuclei that receive bilateral CT projections are also known to receive a number of bilateral prethalamic inputs. Bilateral prethalamic inputs have been demonstrated in the nuclei of the anterior group from the mammillary bodies [38,94,106], in submedius nuclei from the interpolar and caudal divisions of the spinal trigeminal complex [82,108,113,114], in the ventral lateral nuclei from the deep cerebellar nuclei [5,75], in the ventral medial nuclei from the deep cerebellar nuclei and the parabrachial nuclei [5,9,13,75,89] and in the intralaminar nuclei, from the cerebellum, the spinothalamic tracts, the

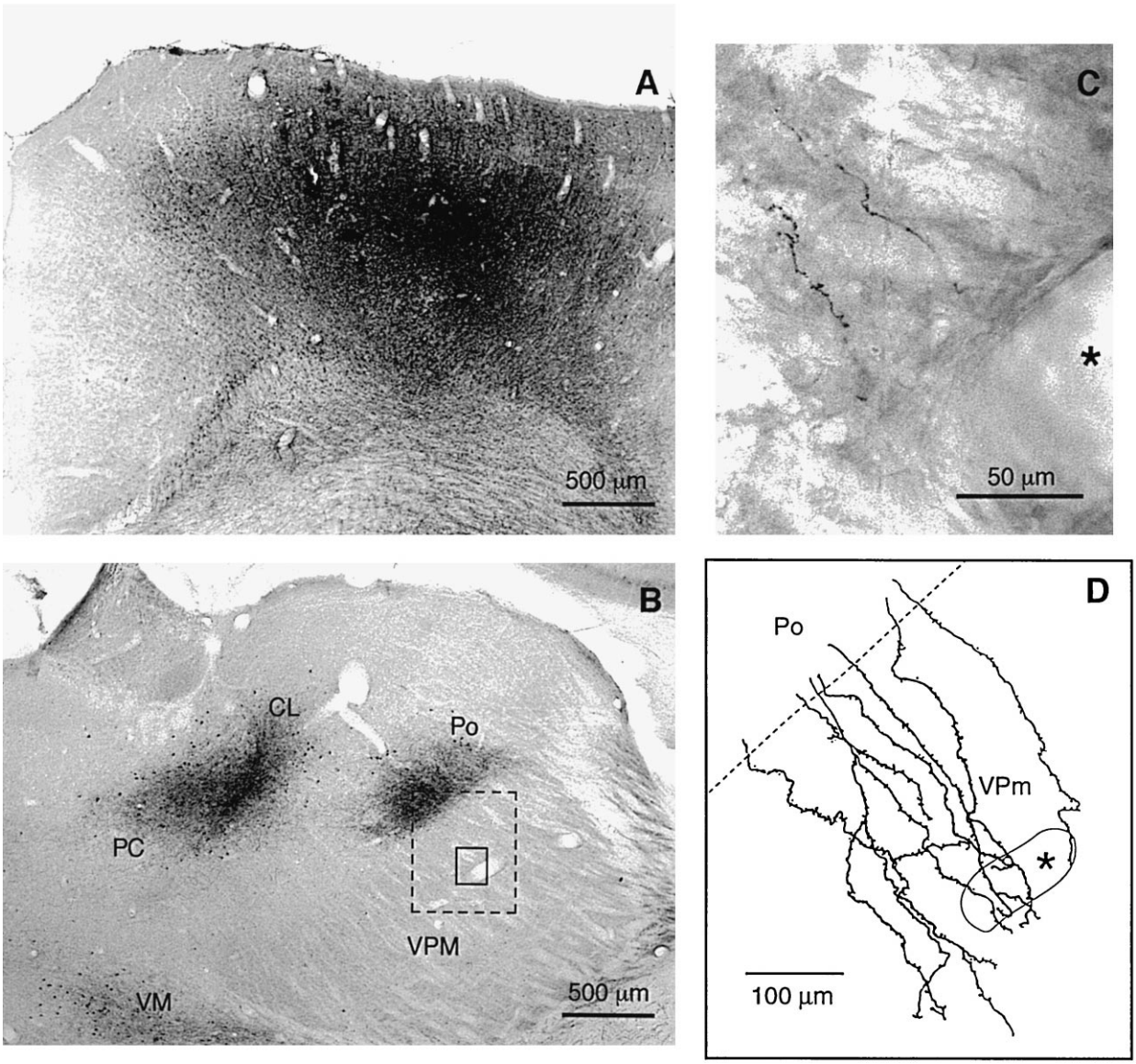


Fig. 13. Retrograde cellular and anterograde axonal labeling in the rat thalamus following a large injection of BDA in the deep layers of the vibrissal motor cortex. The injection site is shown in A and the photomicrograph in B shows the resulting labeling on a frontal section cut through the VPm nucleus (cytochrome oxidase counterstaining). The small boxed area in B is shown in C at a higher magnification. A partial reconstruction of CT fibers descending in the VPm from the overlying Po is shown in D. The region illustrated corresponds to the dashed box in B. Asterisks in C and D mark a reference blood vessel.

deep layers of the superior colliculi and the parabrachial nuclei [5,77,112]. According to the rule of parity, these thalamic nuclei, which are innervated by the two cerebral hemispheres, should receive a prethalamic input from branching axons. Bilateral branching has already been demonstrated for axons of the mammillothalamic tract [38]; in the other systems, this prediction could be easily tested by means of anterograde labeling.

7.4. Developmental implications

The formation of specific neuronal connections in the mammalian central nervous system is thought to rely on two broad mechanisms: those that require neuronal activity (activity-dependent) and those that do not (activity-independent). Growth cones navigate and reach their targets by using a variety of molecular cues generated by mechanisms that are largely activity-independent [101]. These mechanisms bring together multiple inputs with appropriate targets to form initial patterns of connections. From this point on, patterns of activity within these emerging neural circuits take over as the predominant mechanisms that drive the refinement and fine-tuning of synaptic connections [49].

The development of synaptic connections in sensory systems starts at the periphery and proceeds sequentially at successive levels of the pathways. Present evidence indicates that the innervation of thalamic nuclei by prethalamic fibers occurs before that of the cortex by thalamocortical

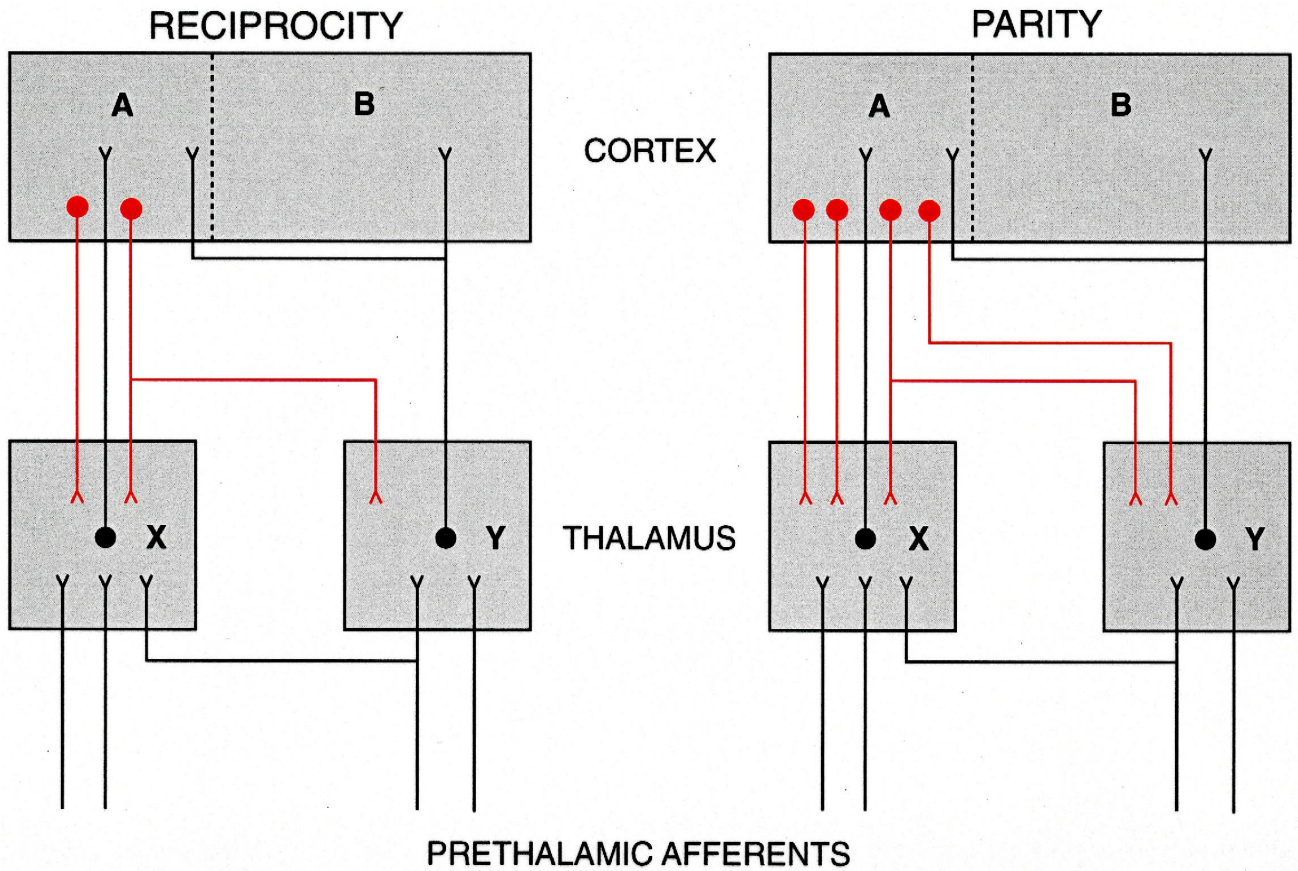


Fig. 14. Comparison between the number of CT cells required by the principle of reciprocity and the rule of parity, respectively. Boxes X and Y represent thalamic nuclei, whereas boxes A and B represent cortical areas. Each prethalamic afferent line corresponds to a different category of fibers.

axons and that of CT projections [57,58,67,92]. In general, the onset of innervations by thalamocortical fibers also precedes that by CT axons. The timing in the establishment of synaptic connections thus appears congruent with the possibility that prethalamic inputs play a role in the final patterning of CT connections.

While the principle of reciprocity suggests that growth cones of CT axons use thalamocortical tracts as cues for pathfinding, a recent study in the visual system has shown that CT and thalamocortical pathways are physically separate during development [71], thus, limiting the possibility of interactions between them. Instead, both pathways may use some common structures, such as subplate neurons, the ganglionic eminence and the perireticular nucleus as intermediate targets for axon pathfinding and target selection [1,33,68,70,72]. Nevertheless, interactions may occur in the cortex between the two pathways during development. In the trigeminal system, thalamocortical fibers can induce barrel-like organization in explants of the visual cortex grafted to the somatosensory area [90]. Early arriving thalamocortical fibers may establish direct contact with CT neurons and induce specific events in such neurons through activity-dependent or independent mechanisms that would push CT fibers towards their proper targets. However, such mechanisms are not applicable for nonreciprocal CT connections unless the blue print of these connections is specified by prethalamic fibers. Innervation of thalamic neurons by ascending fibers may trigger or promote the generation of diffusible factors which act as chemoattractants for incoming CT fibers. Meanwhile, each type of prethalamic neurons may induce the generation of specific surface molecules in the postsynaptic thalamic neurons. Such molecules would interact with specific molecules present on the growth cones of CT axons, and in doing so, participate in target recognition and initiate synaptogenesis thereafter. Thus, the rule of parity implies that the fine-tuning of CT connections relies on the anterograde release of cue signals by prethalamic axons. The recent demonstrations that neurotrophins are transported anterogradely, released, and can alter the phenotype of target cells in the central nervous system, represent important results in support of a parity-based determination of CT connections [4,104].

7.5. Physiology of corticothalamic pathways

In sensory systems, CT pathways are usually considered as feedback loops that modulate the responses of thalamic relay cells to peripheral stimuli. This concept proceeds from the viewpoint that the thalamus is a relay station;

hence, the hypothesis that CT synapses on the distal dendrites of thalamic relay cells should enhance the transfer of peripheral information towards the cortex [52]. In agreement with this hypothesis, many studies have reported that the inactivation or removal of the cortex diminished the spontaneous discharges of relay neurons and their responses to visual or somesthetic stimuli [6,26,31,32,91,102,107,115,116]. These depressive effects, however, proved much less dramatic than what could be anticipated from the elimination of connections of such a numerical importance. A new perspective was opened when Sillito et al. reported that the removal of the visual cortex altered the temporal pattern of sensory-evoked discharges in the lateral geniculate nucleus [95]. In anesthetized cats, they observed that separate pools of relay cells discharged in synchrony when they were co-stimulated by a long light bar moving across their receptive fields. As synchrony was lost after the removal of the cortex, it was concluded that one of the functions of CT cells is to select and group thalamic neurons into thalamocortical ensembles that signal coherent features of visual stimuli. Under the assumption that synchronous firing is the actual mechanism used for binding neuronal ensembles, these results are important because they constitute strong evidence that the thalamus is not merely a state-dependent gateway, but that it takes an active part in the central processing of sensory signals. However, the way by which CT feedback introduces synchrony in the responses of relay cells remains obscure. Indeed, CT cells have slow conducting axons that induce slow-rising excitatory postsynaptic potentials in thalamic neurons [25,69]. Therefore, one does not expect the spike train of CT cells to possess the temporal structure for imposing synchrony on the output of thalamic neurons. The CT feedback could at best increase the excitability of geniculate cells, so permitting the expression of a temporal code already present in retinal afferents. A diffuse excitatory system with a widespread distribution in the geniculate nucleus could possibly exert the same effect, but, and this is one of the main result of Sillito et al.'s study, synchrony occurred mainly between cells of the same type, with respect to both X/Y and on/off-center properties. Conversely, the majority of cells showing no correlation were mixed pairs. In our mind, this is a strong point for the rule of parity, as it suggests specific feedbacks that match the X and Y retinal systems.

7.6. Parity and the notion of feedback

Sensory neurophysiology always proceeds centralwards, its usual approach consists of the determination on how the parameters of stimuli encoded by sensory receptors at the periphery are processed centrally. Because the receptive fields and responses properties of thalamic neurons closely resemble those of prethalamic afferents [43,84], and because thalamic cells exhibit a state-dependent oscillatory activity [97], the thalamus was once considered as a gateway, which is shut during sleep and opened during wakefulness. Along this centralward direction, the axons returned by the cortex stand as feedback loops whose role remains undetermined. Theoretical studies proposed that CT pathways could be involved in functions, such as selective attention, feature selection and grouping. Still, these integrating actions are thought to depend on the configuration of the stimuli that induce matching responses in CT loops. Corticothalamic pathways do make loops with the thalamocortical fibers; however, which elements in a loop form a feedback path is largely a matter of viewpoint. It is obviously legitimate to consider CT pathways as feedback paths in experimental situations in which sensory stimuli are delivered to a head-restrained or anesthetized animal, but when animals hunt for stimuli, the inverse viewpoint likely prevails.

The rule of parity invites to consider CT pathways from a central viewpoint which is more in line with the psychophysical and behavioral evidence that perception is an active process intimately linked to the motor activities of the animal [12,55,65,81]. The pairing of CT and prethalamic innervations postulated by the rule suggests that, in the absence of peripheral inputs, CT afferents may be capable of generating prethalamic-like activity patterns in the thalamus. This possibly occurs during REM sleep. During waking, top–down activation would confer on thalamocortical systems simulation, as well as anticipatory capacities, two functions that are of prime importance for the survival of an animal. Amazingly, in these situations, it is the incoming inputs that would act as a corrective feedback of what is anticipated. Momentary mismatch would produce surprise, orienting reaction and exploratory behavior. This is not to say that all these functions are mainly subserved by CT pathways, but if these projections comply with the rule of parity, they would possess at least the wiring required to support them. Thus, the rule of parity can accommodate both the down–top and top–down viewpoints, each of which may prevail according to the behavioral context.

As a concluding statement in the now classic book, *The Thalamus*, Jones [45] remarked that: ''When we come to consider the inverse relationship, i.e., the nature of the information relayed back from the cortex to the thalamus, we have to confess to almost total ignorance.'' Thirteen years later, we must admit that we still have a very vague idea of what CT pathways do (see the review of Sherman and Guillery [93]). For the moment, the rule of parity seems to possess a broader explanatory and predictive value than the principle of reciprocity. Although future studies may prove it wrong, it is expected that this concept will lead to fruitful researches that will help to understand the role played by these ubiquitous projections.

Acknowledgements

We thank professor R.W. Guillery for helpful comments on the content of this review. This work was

supported by a grant from the Medical Research Council of Canada.

Appendix A. Methods and technical comments

Original results described in Sections 4 and 5 were obtained in adult Sprague–Dawley rats by means of the extracellular and juxtacellular labeling techniques [83]. Experiments were conducted under ketamine (75 mg/kg) and xylazine (5 mg/kg) anesthesia, in accordance with the federally prescribed and university animal care and use guidelines. All surgical, histochemical and cell reconstruction methods were identical to those previously described [15].

In most experiments, biotinylated dextran amine (BDA, mol.wt. = 10 000; Molecular Probes, Eugene, OR) was used as a tracer. The tracer (2% BDA) was dissolved in 0.5 M potassium acetate and ejected by iontophoresis (positive current pulses of 200–600 nA, 500 ms duration, half duty cycle for 30 min). The use of small-sized micropipettes (3–6 μm) resulted in the anterograde labeling of a small number of axons, thus, making possible their reconstruction from serial sections. Like biocytin, BDA stains cell processes in a Golgi-like manner, both tracers seemingly entering into the cells through the small-sized axonal or dendritic processes severed by the micropipette (see discussion by Pinault [83]). This is probably the reason why labeling appears solid and uniform instead of granular as with tracers that can be actively taken up (e.g., lectins or cholera toxin). After extracellular deposits, the labeling of fibers de passage is thus unavoidable. This is not a severe problem with small-sized injections of biocytin because this tracer is readily cleaved by proteolytic enzymes. The injection sites are almost free of extracellular deposit and stained axons can often be followed to their cell of origin. At the sites of BDA injection, however, the extracellular space and neuropil are darkly stained, often obscuring the origin of the labeled axons. In counterpart, the superior stability of BDA allows longer survival periods (3–4 days, even weeks) and a more extensive axonal labeling. When the staining of fibers de passage produces ambiguous results, the problem can be overcome by staining single cells juxtacellularly with BDA. After application of this staining procedure to thalamic neurons, the axon of single cells can often be followed to their most distant termination sites.

References

[1] N.C. Adams, D.A. Lozsadi, R.W. Guillery, Complexities in the thalamocortical and corticothalamic pathways, Eur. J. Neurosci. 9 (1997) 204–209.

[2] A. Agmon, L.T. Yang, E.G. Jones, D.K. O'Dowd, Topological precision in the thalamic projection to neonatal mouse barrel cortex, J. Neurosci. 15 (1995) 549–561.

[3] R.A. Akers, H.P. Killackey, Organization of corticocortical connections in the parietal cortex of the rat, J. Comp. Neurol. 181 (1978) 513–538.

[4] C.A. Altar, N. Cai, T. Bliven, M. Juhasz, J.M. Conner, A.L. Acheson, R.M. Lindsay, S.J. Wiegand, Anterograde transport of brain-derived neurotrophic factor and its role in the brain, Nature 389 (1997) 856–860.

[5] P. Angaut, F. Cicirata, F. Serapide, Topographic organization of the cerebellothalamic projections in the rat: an autoradiographic study, Neuroscience 15 (1985) 389–401.

[6] F.H. Baker, J.G. Malpeli, Effects of cryogenic blockage of visual cortex on the responses of lateral geniculate neurons in the monkey, Exp. Brain Res. 29 (1977) 433–444.

[7] C. Beaulieu, M. Colonnier, Number of neurons in individual laminae of areas 3b, 4γ and 6aα of the cat cerebral cortex, J. Comp. Neurol. 279 (1989) 228–234.

[8] R.M. Beckstead, An autoradiographic examination of corticocortical and subcortical projections of the mediodorsal (prefrontal) cortex in the rat, J. Comp. Neurol. 184 (1979) 43–62.

[9] R.M. Beckstead, J.R. Morse, R. Norgren, The nucleus of the solitary tract in the monkey: projections to the thalamus and brainstem nuclei, J. Comp. Neurol. 190 (1980) 259–282.

[10] H.W. Berendse, H.J. Groenewegen, Restricted cortical termination fields of the midline and intralaminar thalamic nuclei in the rat, Neuroscience 42 (1991) 73–102.

[11] K.L. Bernardo, T.A. Woolsey, Axonal trajectories between mouse somatosensory thalamus and cortex, J. Comp. Neurol. 258 (1987) 542–564.

[12] N.A. Bernstein, The Coordination and Regulation of Movement, Wiley, New York, 1967.

[13] C.H. Block, J.S. Schwartzbaum, Ascending efferent projections of the gustatory parabrachial nuclei in the rabbit, Brain Res. 259 (1983) 1–10.

[14] J. Bourassa, M. Deschênes, Corticothalamic projections from the primary visual cortex in rats: a single fiber study using biocytin as an anterograde tracer, Neuroscience 66 (1995) 253–263.

[15] J. Bourassa, D. Pinault, M. Deschênes, Corticothalamic projections from the cortical barrel field to the somatosensory thalamus in rats: a single fiber study using biocytin as an anterograde tracer, Eur. J. Neurosci. 7 (1995) 19–30.

[16] D.B. Bowling, C.R. Michael, Terminal patterns of single, physiologically characterized optic tract fibers in the cat's lateral geniculate nucleus, J. Neurosci. 4 (1984) 198–216.

[17] C.E. Catsman-Berrevoets, H.G.J.M. Kuypers, Differential laminar distribution of corticothalamic neurons projecting to the VL and the center median: an HRP study in the cynomolgus monkey, Brain Res. 154 (1978) 359–365.

[18] C.E. Catsman-Berrevoets, H.G.J.M. Kuypers, A search for corticospinal collaterals to thalamus and mesencephalon by means of multiple retrograde flourescent tracers in cat and rat, Brain Res. 218 (1981) 15–33.

[19] N.L. Chiaia, R.W. Rhoades, C.A. Bennett-Clarke, S.E. Fish, H.P. Killackey, Thalamic processing of vibrissal information in the rat: I. Afferent input to the medial ventral posterior and posterior nuclei, J. Comp. Neurol. 314 (1991) 201–216.

[20] N.L. Chiaia, R.W. Rhoades, S.E. Fish, H.P. Killackey, Thalamic processing of vibrissal information in the rat: II. Morphological and functional properties of medial ventral posterior nucleus and posterior nucleus neurons, J. Comp. Neurol. 314 (1991) 217–236.

[21] J. Chmielowska, G.E. Carvell, D.J. Simons, Spatial organization of thalamocortical and corticothalamic projection systems in the rat SmI barrel cortex, J. Comp. Neurol. 285 (1989) 325–338.

[22] M. Conley, I.T. Diamond, Organization of the visual sector of the thalamic reticular nucleus in galago, Eur. J. Neurosci. 2 (1990) 211–226.

[23] E.T. Cunningham Jr., S. Levay, Laminar and synaptic organization of the projection from the thalamic nucleus centralis to primary visual cortex in the cat, J. Comp. Neurol. 254 (1986) 66–77.
[24] M. Deschênes, J. Bourassa, D. Pinault, Corticothalamic projections from layer V cells in rat are collaterals of long-range corticofugal axons, Brain Res. 664 (1994) 215–219.
[25] M. Deschênes, B. Hu, Electrophysiology and pharmacology of the corticothalamic input to lateral thalamic nuclei: an intracellular study in cat, Eur. J. Neurosci. 2 (1990) 140–152.
[26] M.E. Diamond, M. Armstrong-James, M.J. Budway, F.F. Ebner, Somatic sensory responses in the rostral sector of the posterior group (Pom) and in the ventral posterior medial nucleus (VPM) of the rat thalamus: dependence on the barrel field cortex, J. Comp. Neurol. 319 (1992) 66–84.
[27] I.T. Diamond, E.G. Jones, T.P.S. Powell, The projection of the auditory cortex upon the diencephalon and brainstem in the cat, Brain Res. 15 (1969) 305–340.
[28] D. Durham, T.A. Woolsey, Effects of neonatal whisker lesion on mouse central trigeminal pathways, J. Comp. Neurol. 223 (1984) 424–447.
[29] R.S. Erzurumlu, H.P. Killackey, Diencephalic projections of the subnucleus interpolaris of the brainstem trigeminal complex in the rat, Neuroscience 5 (1980) 1891–1901.
[30] M. Fabri, H. Burton, Topography of connections between primary somatosensory cortex and posterior complex in rat: a multiple fluorescent tracer study, Brain Res. 538 (1991) 351–357.
[31] E.E. Geisert, A. Langsetmo, F.D. Spear, Influence of the cortico-geniculate pathway on response properties of cat lateral geniculate neurons, Brain Res. 208 (1981) 409–415.
[32] S. Ghosh, G.M. Murray, A.B. Turman, M.J. Rowe, Corticothalamic influences on transmission of tactile information in the ventroposterolateral thalamus of the cat: effect of reversible inactivation of somatosensory cortical areas I and II, Exp. Brain Res. 100 (1994) 276–286.
[33] S. Ghosh, C.J. Shatz, A role for subplate neurons in the patterning of connections from thalamus to neocortex, Development 117 (1993) 1031–1047.
[34] C.D. Gilbert, J.P. Kelly, The projections of cells in different layers of the cat's visual cortex, J. Comp. Neurol. 163 (1975) 81–106.
[35] K.E. Good, H.P. Killackey, Differential laminar distribution of corticothalamic projection neurons in rat primary somatosensory cortex, Soc. Neurosci. Abstr. 17 (1991) 624.
[36] H.J. Groenewegen, H.W. Berendse, The specificity of the nonspecific midline and intralaminar thalamic nuclei, Trends Neurosci. 17 (1994) 53–57.
[37] R.W. Guillery, A study of Golgi preparations from the dorsal lateral geniculate nucleus of the cat, J. Comp. Neurol. 128 (1966) 21–50.
[38] N.G. Guison, A.K. Ahmed, K. Dong, T. Yamadori, Projections from the lateral mammillary nucleus to the anterodorsal thalamic nucleus in the rat, Kobe J. Med. Sci. 41 (1995) 213–220.
[39] A.E. Hallanger, A.I. Levey, H.J. Lee, D.B. Rye, B.H. Wainer, The origins of cholinergic and other subcortical afferents to the thalamus in the rat, J. Comp. Neurol. 262 (1987) 105–124.
[40] M. Herkenham, New perspectives on the organization and evolution of nonspecific thalamocortical projections, in: E.G. Jones, A. Peters (Eds.), Cerebral Cortex, Plenum, 1986, pp. 403–445.
[41] P.V. Hoogland, A. Welker, H. Van der Loos, Organization of the projections from barrel cortex to thalamus in mice studied with *Phaseolus vulgaris*-leucoagglutinin and HRP, Exp. Brain Res. 68 (1987) 73–87.
[42] P.V. Hoogland, F.G. Wouterlood, E. Welker, H. Van der Loos, Ultrastructure of giants and small thalamic terminals of cortical origin: a study of the projections from the barrel cortex in mice using *Phaseolus vulgaris*-leucoagglutinin (PHA-L), Exp. Brain Res. 87 (1991) 159–172.
[43] D.H. Hubel, T.N. Weisel, Integrative action in the cat's lateral geniculate body, J. Physiol. London 155 (1961) 385–398.
[44] K.F. Jensen, H.P. Killackey, Terminal arbors of axons projecting to the somatosensory cortex of the adult rat: I. The normal morphology of specific thalamocortical afferents, J. Neurosci. 7 (1987) 3529–3543.
[45] E.G. Jones, The Thalamus, Plenum, New York, 1985.
[46] E.G. Jones, T.P.S. Powell, An electron microscopic study of the mode of termination of cortico-thalamic fibres within the sensory relay nuclei of the thalamus, Proc. R. Soc. London B Biol. Sci. 172 (1969) 173–185.
[47] S.S. Kaitz, R.T. Robertson, Thalamic connections with limbic cortex: II. Corticothalamic projections, J. Comp. Neurol. 195 (1981) 527–545.
[48] L.C. Katz, Local circuitry of identified projection neurons in cat visual cortex brain slices, J. Neurosci. 7 (1987) 1223–1249.
[49] L.C. Katz, C.J. Shatz, Synaptic activity and the construction of cortical circuits, Science 274 (1996) 1133–1138.
[50] H.P. Killackey, Anatomical evidence for cortical subdivisions based on vertically discrete thalamic projections from the ventral posterior nucleus to cortical barrels in the rat, Brain Res. 51 (1973) 326–331.
[51] H.P. Killackey, S. Leshin, The organization of specific thalamocortical projections to the posteromedial barrel subfield of the rat somatic sensory cortex, Brain Res. 86 (1975) 469–472.
[52] C. Koch, The action of the corticofugal pathway on sensory thalamic nuclei: a hypothesis, Neuroscience 23 (1987) 399–406.
[53] C. Koch, S.M. Sherman, The control of retinogeniculate transmission in the mammalian lateral geniculate nucleus, Exp. Brain Res. 63 (1988) 1–20.
[54] K.A. Koralek, K.F. Jensen, H.P. Killackey, Evidence for two complementary patterns of thalamic input to the rat somatosensory cortex, Brain Res. 463 (1988) 346–351.
[55] M.F. Land, D.N. Lee, Where we look when we steer, Nature 369 (1994) 742–744.
[56] P.W. Land, S.A. Buffer Jr., J.D. Yaskosky, Barreloids in adult rat thalamus: three-dimensional architecture and relationship to somatosensory cortical barrels, J. Comp. Neurol. 355 (1995) 573–588.
[57] C.A. Leamy, L.R. Marotte, P.M. Waite, Timecourse of development of the wallaby trigeminal pathway: II. Brainstem to thalamus and the emergence of cellular aggregations, J. Comp. Neurol. 364 (1996) 494–514.
[58] C.A. Leamy, L.R. Marotte, P.M. Waite, Timecourse of development of the wallaby trigeminal pathway: III. Thalamocortical and corticothalamic projections, J. Comp. Neurol. 387 (1997) 194–214.
[59] C.M. Leonard, The prefrontal cortex of the rat: I. Cortical projections of the mediodorsal nucleus, II. Efferent connections, Brain Res. 12 (1969) 321–343.
[60] S. Levay, H. Sherk, The visual claustrum of the cat: I. Structure and connections, J. Neurosci. 1 (1981) 956–980.
[61] M. Lévesque, S. Gagnon, A. Parent, M. Deschênes, Axonal arborizations of corticostriatal and corticothalamic fibers arising from the second somatosensory area in the rat, Cerebral Cortex 6 (1996) 759–770.
[62] X.-B. Liu, C.N. Honda, E.G. Jones, Distribution of four types of synapse on physiologically identified relay neurons in the ventral posterior thalamic nucleus of the cat, J. Comp. Neurol. 352 (1995) 69–91.
[63] R. Lorente de No, La corteza cerebral del raton, Trab. Lab. Invest. Biol. Univ. Madrid 20 (1922) 1–38.
[64] S.-M. Lu, R.C.-S. Lin, Thalamic afferents of the rat barrel cortex: a light- and electron-microscopic study using *Phaseolus vulgaris*-leucoagglutinin as an anterograde tracer, Somatosens. Mot. Res. 10 (1993) 1–16.
[65] D.G. Mackay, The Organization of Perception and Action, Springer Verlag, New York, 1987.
[66] K. Majorossy, A. Kiss, Specific patterns of neuron arrangement and of synaptic articulation in the medial geniculate body, Exp. Brain Res. 26 (1976) 1–17.
[67] L.R. Marotte, C.A. Leamy, P.M. Waite, Timecourse of develop-

ment of the wallaby trigeminal pathway: III. Thalamocortical and corticothalamic projections, J. Comp. Neurol. 387 (1997) 194–214.
[68] S.K. McConnell, A. Ghosh, C.J. Shatz, Subplate pioneers and the formation of descending connections from cerebral cortex, J. Neurosci. 14 (1994) 1892–1907.
[69] D.A. McCormick, M. von Krosigk, Corticothalamic activation modulates thalamic firing through glutamate metabotropic receptors, Proc. Natl. Acad. Sci. U.S.A. 89 (1992) 1774–1778.
[70] C. Metin, P. Godement, The ganglionic eminence may be an intermediate target for corticofugal and thalamocortical axons, J. Neurosci. 16 (1996) 3219–3225.
[71] B. Miller, L. Chou, B.L. Finlay, The early development of thalamocortical and corticothalamic projections, J. Comp. Neurol. 335 (1993) 16–41.
[72] J. Mitrofanis, R.W. Guillery, New views on the thalamic reticular nucleus in the adult and developing brain, Trends Neurosci. 16 (1993) 240–245.
[73] M. Molinari, D. Minciacchi, M. Bentivoglio, G. Macchi, Efferent fibers from the motor cortex terminate bilaterally in the thalamus of rats and cats, Exp. Brain Res. 57 (1985) 305–312.
[74] P.C. Murphy, A.M. Sillito, Functional morphology of the feedback pathway from area 17 of the cat visual cortex to the lateral geniculate nucleus, J. Neurosci. 16 (1996) 1180–1192.
[75] K. Nakano, T. Takimoto, T. Kayahara, Y. Takeuchi, Y. Kobayashi, Distribution of cerebellothalamic neurons projecting to the ventral nuclei of the thalamus: an HRP study in the cat, J. Comp. Neurol. 194 (1980) 427–439.
[76] M.A.L. Nicolelis, J.H. Chapin, C.R.S. Lin, Development of direct projections from the zona incerta to the somatosensory cortex of the rat, Neuroscience 65 (1995) 609–631.
[77] K. Niimi, M. Kusunose, K. Ono, M. Yanagihara, Brainstem afferents to the intralaminar nuclei of the cat thalamus studied by the horseradish peroxidase method, J. Hirnforsch. 31 (1990) 107–122.
[78] S. Oda, Ultrastructure and distribution of corticothalamic fiber terminals from the posterior cingulate cortex and the presubiculum to the anteroventral thalamic nucleus in the rat, Brain Res. Bull. 42 (1997) 485–491.
[79] H. Ojima, Terminal morphology and distribution of corticothalamic fibers originating from layers 5 and 6 of cat primary auditory cortex, Cerebral Cortex 4 (1994) 646–663.
[80] G. Paxinos, C. Watson, The Rat Brain in Stereotaxic Coordinates, 2nd edn., Academic Press, Sydney, 1986.
[81] L. Peper, R.J. Bootsma, D.R. Mestre, F.C. Bakker, Catching balls: how to get the hand to the right place at the right time, J. Exp. Psychol. 20 (1994) 591–612.
[82] M. Peschanski, Trigeminal afferents to the diencephalon in the rat, Neuroscience 12 (1984) 465–487.
[83] D. Pinault, A novel single-cell staining procedure performed in vivo under electrophysiological control: morpho-functional features of juxtacellularly labeled thalamic cells and other central neurons with biocytin or neurobiotin, J. Neurosci. Methods 65 (1996) 113–136.
[84] G.F. Poggio, V.B. Mountcastle, The functional properties of ventrobasal thalamic neurons studied in unanesthetized monkeys, J. Neurophysiol. 26 (1963) 775–806.
[85] R.L. Reep, S.S. Winans, Efferent connections of dorsal and ventral agranular insular cortex in the hamster, *Mesocricetus auratus*, Neuroscience 7 (1982) 2609–2635.
[86] K.S. Rockland, Further evidence for two types of corticopulvinar neurons, Neuroreport 5 (1994) 1865–1868.
[87] E.M. Rouiller, F. Liang, V. Moret, M. Weisendanger, Patterns of corticothalamic terminations following injection of *Phaseolus vulgaris*-leucoagglutinin (PHA-L) in the sensorimotor cortex of the rat, Neurosci. Lett. 125 (1991) 93–97.
[88] E.M. Rouiller, E. Welker, Morphology of thalamic afferents from the auditory cortex of the rat; a *Phaseolus vulgaris*-leucoagglutinin (PHA-L) tracing study, Hear. Res. 56 (1991) 179–190.
[89] C.B. Saper, A.F. Loewy, Efferent connections of the parabrachial nucleus in the rat, Brain Res. 197 (1980) 291–318.
[90] B.L. Schlaggar, D.D. O'Leary, Potential of visual cortex to develop an array of functional units unique to somatosensory cortex, Science 252 (1991) 1556–1560.
[91] F. Schmielau, W. Singer, The role of visual cortex for binocular interactions in the cat lateral geniculate nucleus, Brain Res. 120 (1977) 354–361.
[92] C.J. Shatz, The prenatal development of the cat's retinogeniculate pathway, J. Neurosci. 3 (1983) 482–499.
[93] S.M. Sherman, R.W. Guillery, Functional organization of thalamocortical relays, J. Neurophysiol. 76 (1996) 1367–1395.
[94] H. Shibata, Topographic organization of subcortical projections to the anterior thalamic nuclei in the rat, J. Comp. Neurol. 323 (1992) 117–127.
[95] A.M. Sillito, H.E. Jones, G.L. Gerstein, D.C. West, Feature-linked synchronization of thalamic relay cell firing induced by feedback from the visual cortex, Nature 369 (1994) 479–482.
[96] G. Somogyi, F. Hajdu, T. Tomböl, Ultrastructure of the anterior ventral and anterior medial nuclei of the cat thalamus, Exp. Brain Res. 31 (1978) 417–431.
[97] M. Steriade, M. Deschênes, The thalamus as a neuronal oscillator, Brain Res. Rev. 8 (1984) 1–63.
[98] M. Sur, S.M. Sherman, Retinogeniculate terminations in cat: morphological differences between X and Y cell axons, Science 218 (1982) 389–391.
[99] M. Sur, M. Esguerra, P.E. Garraghty, M.F. Kritzer, S.M. Sherman, Morphology of physiologically identified retinogeniculate X- and Y-axons in the cat, J. Neurophysiol. 58 (1987) 1–32.
[100] N. Tamamaki, D.J. Uhlrich, S.M. Sherman, Morphology of physiologically identified retinal X and Y axons in the cat's thalamus and midbrain as revealed by intra-axonal injection of biocytin, J. Comp. Neurol. 354 (1994) 583–607.
[101] M. Tessier-Lavigne, C.S. Goodman, The molecular biology of axon guidance, Science 274 (1996) 1123–1133.
[102] T. Tsumoto, O.D. Creutzfeldt, C.R. Legendy, Functional organization of the corticofugal system from visual cortex to lateral geniculate nucleus in the cat, Exp. Brain Res. 32 (1978) 345–364.
[103] W.M. Usrey, D. Fitzpatrick, Specificity in the axonal connections of layer VI neurons in Tree Shrew striate cortex: evidence for distinct granular and supragranular systems, J. Neurosci. 16 (1996) 1203–1218.
[104] C.S. von Bartheld, M.R. Byers, R. Williams, M. Bothwell, Anterograde transport of neurotrophins and axodendritic transfer in the developing visual system, Nature 379 (1996) 830–833.
[105] B.R. Wang, P.T. Ohara, Convergent projections of trigeminal afferents from the principal nucleus and subnucleus interpolaris upon rat ventral posteromedial thalamic neurons, Brain Res. 629 (1993) 253–259.
[106] K. Watanabe, E. Kawana, A horseradish peroxidase study on the mammillothalamic tract in the rat, Acta Anat. Basel 108 (1980) 394–401.
[107] L. Widén, C. Ajmone-Marsan, Effects of corticopetal and corticofugal impulses upon single elements of the dorsal lateral geniculate nucleus, Exp. Neurol. 3 (1960) 468–561.
[108] M.N. Williams, D.S. Zahm, M.F. Jacquin, Differential foci and synaptic organization of the principal and spinal trigeminal projections to the thalamus in the rat, Eur. J. Neurosci. 6 (1994) 429–453.
[109] J.A. Winer, D.T. Larue, Patterns of reciprocity in auditory thalamocortical and corticothalamic connections: study with horseradish peroxidase and autoradiographic methods in the rat medial geniculate body, J. Comp. Neurol. 257 (1987) 282–315.
[110] S.P. Wise, E.G. Jones, Developmental studies of thalamocortical and commissural connections in the rat somatic sensory cortex, J. Comp. Neurol. 178 (1978) 187–208.
[111] N.J. Woolf, L.L. Butcher, Cholinergic systems in the rat brain: III. Projections from the pontomesencephalic tegmentum to the thala-

mus, tectum, basal ganglia and basal forebrain, Brain Res. Bull. 16 (1986) 603–637.
[112] D.S.G. Yamasaki, G.M. Krauthamer, R.W. Rhoades, Superior collicular projections to intralaminar thalamus in rat, Brain Res. 378 (1986) 223–233.
[113] A. Yoshida, J.O. Dostrovsky, C.Y. Chiang, The afferent and efferent connections of the nucleus submedius in the rat, J. Comp. Neurol. 324 (1992) 115–133.
[114] A. Yoshida, J.O. Dostrovsky, B.J. Sessle, C.Y. Chiang, Trigeminal projections to the nucleus submedius of the thalamus in the rat, J. Comp. Neurol. 307 (1991) 609–625.
[115] B. Yuan, T.J. Morrow, K.L. Casey, Responsiveness of ventrobasal thalamic neurons after suppression of S1 cortex in the anesthetized rat, J. Neurosci. 5 (1985) 2971–2978.
[116] B. Yuan, T.J. Morrow, K.L. Casey, Corticofugal influences of S1 cortex on ventrobasal thalamic neurons in the awake rat, J. Neurosci. 6 (1986) 3611–3617.
[117] Z.-W. Zhang, M. Deschênes, Intracortical axonal projections of lamina VI cells of the primary somatosensory cortex in the rat: a single-cell labeling study, J. Neurosci. 17 (1997) 6365–6379.
[118] Z.-W. Zhang, M. Deschênes, Projections to layer 6 of the posteromedial barrel field in the rat: a reappraisal of the role of corticothalamic pathways, Cerebral Cortex, in press.