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REVIEW ARTICLE

A comparative analysis of the morphology of corticothalamic projections in mammals

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ABSTRACT: Recent anatomical tracing methods have revealed new principles underlying the organization of corticothalamic connections in the mammalian nervous system. These data demonstrated the distribution of two types of synaptic contacts in the corticothalamic projection: small (<1 μm) and giant (2–10 μm) axon terminals. We compare the organization of corticothalamic projections in the auditory, somatosensory, visual, and motor systems of a variety of mammalian species, including the monkey. In all these systems and species, both types of corticothalamic terminals have been observed. Small endings formed the major corticothalamic terminal field, whereas giant terminals were less numerous and formed additional terminal fields together with small terminals. After comparing their spatial distribution, as well as the degree of reciprocity between the corticothalamic and thalamocortical projections, different roles are proposed for small and giant endings. Small terminals are typically present in the projection serving the feed-back control of the cerebral cortex on the thalamic nucleus from which it receives its main projection. In contrast, giant terminals are involved in feed-forward projections by which activity from a cortical area is distributed, via the thalamus, to other parts of the cerebral cortex. The cross-species and cross-systems comparison reveals differences in the mode of feed-forward projection, which may be involved in the activation of other parts of the same cortical area or form part of a projection that activates *other* cortical areas. © 2001 Elsevier Science Inc.

KEY WORDS: Rodent, Cat, Monkey, Tracing, Thalamus, Auditory cortex, Visual cortex, Motor cortex, Somatosensory cortex.

INTRODUCTION

It is well established in mammals that the ascending information reaching the cerebral cortex derives primarily from thalamic relay nuclei. The prominent thalamocortical (TC) projection is associated with an even denser reciprocal corticothalamic (CT) projection, allowing the cerebral cortex to exert what is generally considered a descending *feed-back* control on the thalamus. So far, as judged by the number of reports available in the literature, the TC projection system has received more attention than the reciprocal CT projection system. However, numerically, CT axons constitute the major source of input to sensory relay thalamic neurons, at least in the lateral [40,48] and medial [4,51,64] geniculate nuclei.

For the motor system and most sensory systems, the topology of the CT projection has been established in detail for a long time. The neuroanatomical studies were based on the method of axonal degeneration, whereas more recent studies have used retrograde tracers such as horseradish peroxidase (HRP), wheat germ agglutinin conjugated to HRP (WGA-HRP), and fluorescent markers. Examination of the tracing studies available in the literature revealed the extreme complexity of the topology of the CT projection. For instance, in the cat, 650 CT connections link cortical areas with 42 thalamic nuclei (see [72] for review). Recently, modern anterograde tracers were introduced such as biocytin, *Phaseolus vulgaris*-leucoagglutinin (PHA-L) and dextrans [mainly biotinylated dextran amine (BDA)]. The advantage of these tracers is that axons can be followed from the injection site to the terminal fields. This property had at least three important consequences for the interpretation of neuroanatomical data. First, these tracers provided a higher resolution in the analysis of the trajectory of axons. Second, and more importantly, the tracers labeled axon collaterals, a property essential to address the issue of divergence in neural connectivity. Third, these anterograde tracers offered the possibility to visualize the detailed morphology of axon terminals (putative presynaptic boutons). The goal of the present report is to review the data derived from neuroanatomical studies based on such sensitive anterograde tracers, in order to establish the fine morphological characteristics and the topographical distribution of the CT axon terminals.

Two main types of CT terminals can be observed when cortex is injected with an anterograde tracer: small endings (usually <1 μm in diameter) and giant endings (usually 2–5 μm in diameter). Our goal is to compare across mammals and across systems (e.g., auditory, visual, somatosensory, and motor) the topographical distribution of the small and giant CT endings in the thalamus. More precisely, the following questions will be addressed: are small and giant endings mixed or segregated? In a given system,

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do they both originate from all cortical areas? Do they arise from the same CT neurons? Across systems and mammals, do we find a common principle of CT projection with respect to the morphology of endings and their topographical distribution? On the basis of the answers to these questions, we will speculate on specific roles for small and giant endings in the processing of information at the thalamic and cortical levels.

OVERVIEW OF THE ORGANIZATION OF THE MAMMALIAN CT PROJECTIONS

Auditory Cortex

The organization of the CT projection originating from the auditory cortex will be reviewed in three species, the rat, cat, and macaque monkey. Emphasis will be put on the cat, which represented for a long time the animal model of choice for the auditory system. However, more recently, the monkey model has received more attention, essentially for studies at the level of the auditory cortex. For both cat and monkey, the properties of the CT projection will be compared across the multiple auditory cortical areas.

Cat data. The topographical organization of the auditory CT projection is best defined in the cat, as initially established by means of anterograde degeneration [21,56], anterograde autoradiography [4,56], and retrograde HRP or fluorescent tracing data [36,64,94]. The target nuclei of the CT projections originating from distinct auditory cortical areas are summarized in diagram form in Fig. 1. A more detailed description of the organization of this projection is given below, as derived from studies using modern anterograde tracers, that provide better resolution and structure. As a result of injection of an anterograde tracer (biocytin) in distinct auditory cortical areas, it was possible to compare the CT projections originating from the primary (AI), the anterior (AAF), the posterior (PAF), and the secondary (AII) auditory cortical fields of the cat [9]. The tonotopically organized areas AI, AAF, and PAF exhibit a similar pattern of projection. They send a major CT projection to the ventral division of the medial geniculate body (vMGB), mainly in the so-called pars lateralis. This major CT projection terminates with axon terminals of small size. In vMGB, terminal fields originating from PAF are located more caudally than those deriving from AI and AAF. The same rostrocaudal distribution was found for the TC projection, with TC neurons projecting to PAF located more caudally in vMGB than TC neurons projecting to AAF and AI [63]. The precise location of the CT terminal fields is consistent with the tonotopic organization of vMGB, thus matching the best frequency (BF) zone in AAF, AI, or PAF where the tracer injection was deposited [9]. In addition, AAF, AI, and PAF also send a projection, though quantitatively smaller, to the medial division of the medial geniculate body (mMGB), and these fibers also terminate with small endings [9] (see Fig. 1). Finally, AAF, AI, and PAF are the source of a quantitatively minor projection directed towards the dorsal division of the medial geniculate body (dMGB), and these axon terminals are represented by both small and giant endings. The pattern of the CT projection originating from the tonotopic areas AI, AAF, and PAF is summarized in Fig. 2.

In sharp contrast, the CT projection originating from AII terminates mainly in dMGB [9]. The majority of these axon terminals are also represented by small endings, distributed in two separate clusters corresponding to the two subdivisions of the dMGB, namely the (superficial) dorsal nucleus (D) and the deep dorsal nucleus (DD). In the latter two nuclei, the main projection formed by small endings is accompanied by giant axon terminals, which are clearly less numerous than the small endings. In addition to its projection to the dMGB, AII also sends a projection to the mMGB, formed exclusively by small endings. AII does not project to the vMGB. In summary, the topology of the CT projections differs significantly between the tonotopically organized cortical areas AAF, AI, and PAF on one hand and the non-tonotopic area AII on the other hand (Fig. 1).

In a study based on the use of the anterograde tracer BDA, Winer et al. [92] confirmed previous results [9] and provided additional data regarding other auditory cortical areas in the cat. Giant CT endings were found in dMGB and in the suprageniculate nucleus, and these endings originated from the two areas located more laterally than AII, namely the insular cortex and the temporal cortex. Winer et al. [92] claimed that all auditory cortical areas give rise to a number of giant endings higher than that reported previously (see above). This numerical difference may be due to the larger size of the BDA injections performed by Winer et al. [92] as compared to the biocytin injections performed by Bajo et al. [9]. In addition, BDA may be a more effective anterograde tracer than biocytin, particularly over long distances. Another important observation of the study by Winer et al. [92] was that the CT giant endings were distributed in zones of the MGB matching the territories where other large terminals from a different origin were found. These large terminals were immunostained for γ-aminobutyric acid, but their origin [from the reticular nucleus of the thalamus (RT), the inferior colliculus, or intrinsic Golgi type II cells] remains uncertain [92].

Based on injections of PHA-L or biocytin in AI at various depths (in layers V or VI), it was observed that in this cortical area small endings (distributed mainly in vMGB) originate from neurons located in layer VI, whereas giant endings arise from neurons located in layer V [51]. These two populations of cells can be further distinguished on the basis of the morphology and size of their soma and dendrites, as well as the pattern of their intracortical axon collateralization [52]. The different laminar location of neurons giving rise to small versus giant endings was demonstrated only in AI [51]. In Fig. 1, the same laminar arrangement was extended to AAF, AII, and PAF, as well as to the rat primary auditory cortex, but the validity of such an extension remains to be demonstrated. As indicated in Fig. 1 for the rat and cat, neurons in layer V were also found to be the origin of the corticotectal projection terminating in the inferior colliculus [5,46,71,81], where they form large endings as in the dMGB [51]. The corticofugal projection originating from layer V neurons extends even further to the periphery, forming a corticobulbar projection terminating in the superior olivary complex and cochlear nucleus [24, 87,88].

Rat data. In the auditory system of the rat, data regarding the morphology of CT terminals are available only for the equivalent of AI, namely the area Te1 [66]. As in the cat, the main target nucleus is the vMGB where, after a PHA-L injection in Te1, only small endings were observed. Small endings, although less numerous, were also found in the dMGB and in the mMGB. Giant endings were also present after injection in Te1, in the dMGB. Therefore, the location of the CT giant endings originating in the rat from Te1 occupies the same location (dMGB) as in the cat after an injection in AI (Fig. 1). A major difference between rat and cat regarding the giant endings was that in the former species they were spherical whereas in the cat they exhibited a finger-like appearance. The precise topography and morphology of CT terminals originating from areas Te2 and Te3 in the rat remain to be established.

Monkey data. In the macaque monkey, the topography of the CT projections originating from the auditory cortical areas was described in detail [55]. The data were derived from neuroanatomical tracing studies based on retrograde fluorescent tracers injected in the thalamus, or anterograde isotope-labeled amino acids injected in the cortex (Fig. 1). Unfortunately, the latter tracer

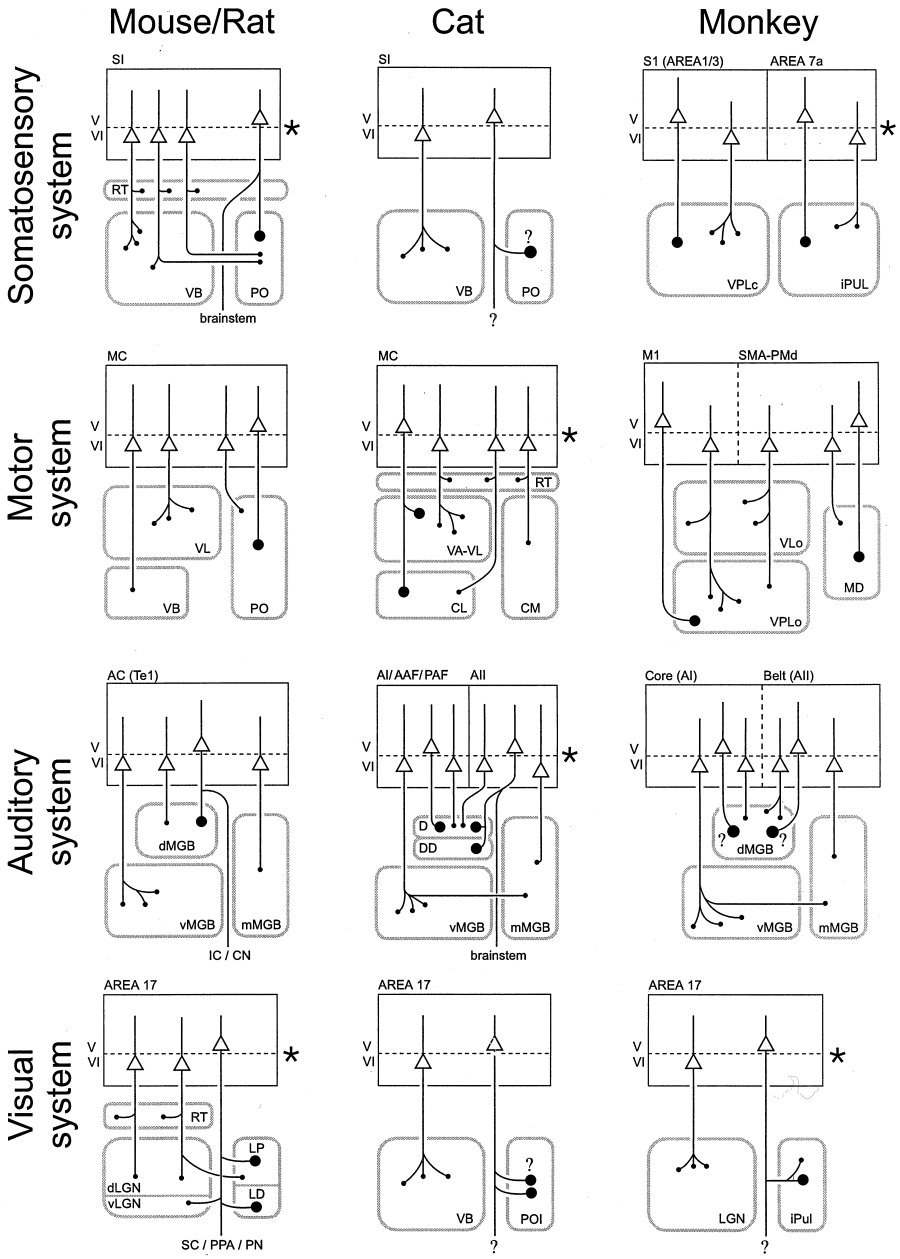

FIG. 1. A schematic representation of the topography of the corticothalamic (CT) projection in rodents, cat, and macaque monkeys for the somatosensory, motor, auditory, and visual cortices (four rows from top to bottom). Black rectangles are for cortical areas whereas boxes in gray are for thalamic nuclei. See list of abbreviations. In the cortex, open triangles represent pyramidal CT neurons, that are distributed between layers V and VI. An asterisk placed at the right of a rectangle (cortical area) signifies that precise data are available that demonstrate that layer V neurons give rise to giant endings and layer VI neurons to small endings. In the thalamus, small filled circles represent small CT endings whereas large filled circles represent giant endings. The reticular nucleus of the thalamus (RT) was represented here only when there are data demonstrating at the single cell level that layer V neurons do not send collaterals to RT whereas layer VI neurons do. In the other cases, where the laminar difference with respect to collateralization has not yet been strictly demonstrated, RT was not drawn for simplification. Question marks for the auditory system of the monkey indicate that the presence of giant endings has not been confirmed using anterograde tracers that provide cellular resolution. See text for citations of studies from which data were taken to generate this schematic representation of the CT projection. Abbreviations: AAF, anterior auditory cortical field; AI, primary auditory cortical field; AII, secondary auditory cortical field; CL, central lateral nucleus; CM, centralmedial nucleus; CN, cochlear nucleus; D, superficial nucleus of dorsal division of the medial geniculate body; DD, deep nucleus of dorsal division of the medial geniculate body; dLGN, dorsal part of the lateral geniculate nucleus; dMGB, dorsal division of the medial geniculate body; IC, inferior colliculus; iPul, inferior pulvinar nucleus (medial division); LGN, lateral geniculate nucleus; MC, motor cortex; MD, mediodorsal nucleus; mMGB, medial division of the medial geniculate body; M1, primary motor cortical area; PPA, posterior pretectal area; PAF, posterior auditory cortical field; PMd, dorsal premotor cortex; PN, pontine nuclei; PO, posterior nucleus of the thalamus; POl, lateral division of the posterior nucleus; SC, superior colliculus; SI, primary somatosensory cortex; SMA, supplementary motor cortical area; VA-VL, ventroanterior-ventrolateral complex; VB, nucleus ventrobasalis; VL, ventrolateral nucleus; Vlo, ventral lateral nucleus, oral part; vLGN, ventral lateral geniculate nucleus; vMGB, ventral division of the medial geniculate body; VPLc, ventroposterolateral nucleus, caudal part; VPLo, ventroposterolateral nucleus, oral part.

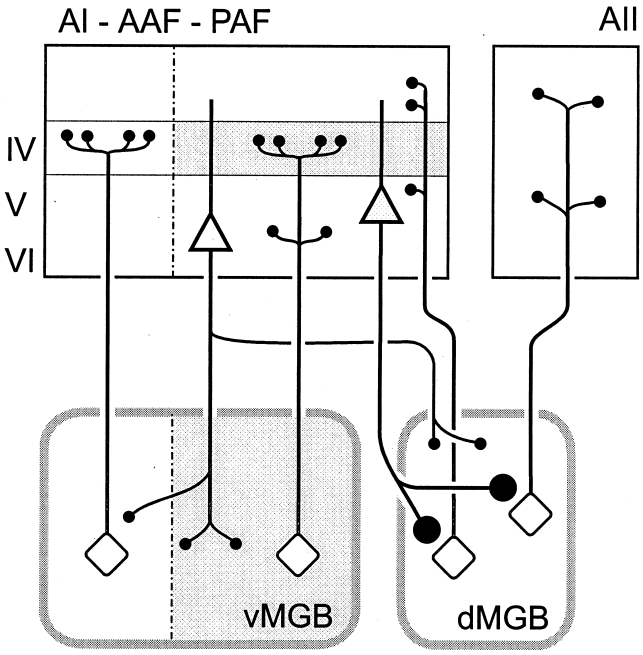

FIG. 2. A schematic representation of cortico-thalamo-cortical loops for the tonotopically organized auditory cortical areas primary (AI), anterior (AAF), and posterior (PAF) auditory cortical fields in the cat. Black rectangles represent cortical areas whereas boxes in gray are for thalamic nuclei. Corticothalamic (CT) neurons are represented by open triangles whereas thalamocortical (TC) neurons appear as open diamonds. Axon terminals are represented by filled circles (small and large). The cortical layers IV, V, and VI are indicated. As a result of tracer injection in a portion of AI, AAF or PAF (gray zone in the top rectangle), anterograde labeling is found in the ventral division of the medial geniculate body (vMGB), in the form of small endings (small filled circles). The territory of anterograde labeling does not exactly match the territory of retrograde labeling (TC cells represented by open diamonds). The zone of matching (gray zone in the gray box representing the vMGB) is the support for a feed-back control exerted by AI, AAF and PAF on the vMGB. The zone of non-matching (white zone in the gray box representing the vMGB) is the support for a "local" feed-forward projection to a zone of cortex immediately adjacent to the injected zone, via the thalamus (see text). A territory of anterograde labeling is also found in the dorsal division of the MGB (dMGB), consisting of giant endings (large filled circles) coming from layer V neurons and small endings coming probably from layer VI neurons. This projection to the dMGB represents additional support for feed-back control but it also provides evidence for a long distance feed-forward projection. Indeed it links AI, AAF, or PAF to secondary auditory cortical field (AII) via the dMGB, the latter representing the main source of ascending inputs to AII (see text). For simplification, the projection using small endings from AI, AAF, and PAF to the mMGB is not represented here.

does not allow individual axons to be visualized and therefore the morphology of axon terminals could not be determined. With respect to the laminar origin of the CT projection, Pandya et al. [55] observed a vast majority of CT neurons in layer VI; however, a few scattered CT cells were found in layer V. The latter neurons might be the source of giant axon terminals in the monkey MGB. The topographical arrangement of the CT projection in the macaque monkey appears to be fairly comparable to that of the cat (Fig. 1). A main projection derives from the tonotopic areas (core of the auditory cortex) and terminates in the vMGB, whereas the belt areas (corresponding to secondary auditory cortical fields) project mainly to the dMGB [55]. As in the cat, both the core and belt areas project to the mMGB (Fig. 1). In addition, the core area sends a projection to the dMGB [55]. Therefore, by analogy with the cat, one might predict that giant endings in monkeys may be located in the dMGB, originating from the core and belt cortical areas. However, this assumption remains to be demonstrated in future tracing experiments using adequate anterograde tracers (see question marks in Fig. 1).

One should mention that most auditory CT projections also terminate in the auditory sector of the RT [9,51,66]. In the RT, the axon terminals correspond to small endings. It has been demonstrated in the cat that the projections terminating in the RT are collaterals of the axons directed to the MGB, at least those originating from AI [65]. The other auditory cortical areas in the cat (AAF, PAF, and AII) also send a projection to the auditory sector of the RT. It remains to be demonstrated whether these fibers are collaterals of CT axons, although this is very likely considering the organization of the CT projection deriving from AI.

Visual Cortex

Comparison across species. The primary visual cortex in mammals projects to the dorsal part of the lateral geniculate nucleus (dLGN) from which it receives its main thalamic input. The first electron microscopic demonstration of this projection was made by Jones and Powell [35] in the cat using the anterograde degeneration method. Besides the projection to the dLGN (named "first order nucleus" by Guillery, [28]), the primary visual cortex also projects to the RT, to the ventral part of the lateral geniculate nucleus (vLGN) and to the "higher order thalamic nuclei" [28] such as the lateral dorsal nucleus (LD) and the lateral posterior nucleus (LP) in the rat and cat; the inferior pulvinar nucleus (iPul) in the macaque monkey. These CT projections are summarised in Fig. 1.

Mathers [42] was the first to demonstrate at the ultrastructural level that, in the squirrel monkey, the projection from the peristriate cortex to the iPul was made by two types of terminals: small (RS) and large (RL) axon terminals, that both make asymmetric contacts with dendritic profiles. Robson and Hall [59,60] compared the morphology of cortical terminals in dLGN to that in the pulvinar in the grey squirrel. They subdivided the pulvinar into three parts and showed that its rostro-medial subdivision received cortical projections from the primary and secondary visual cortex. The ultrastructural analysis revealed that the cortical projection to the dLGN was made by RS cortical terminals whereas the rostro-medial subdivision of the pulvinar received RS *and* RL cortical terminals. This study provided evidence that the large terminals originate from the primary visual cortex, while the projection from areas 18 and 19 is made by small terminals. These findings were obtained with anterograde degeneration. More recent tracing studies confirmed the ultrastructure of these projections in the inferior pulvinar nucleus of the owl monkey and the lateral posterior nucleus of the cat [23].

Modern tracing methods were used to study the spatial distribution of CT axons at the light microscopic level in the visual pathway of various species. Rockland [62] made injections of PHA-L in the primary visual cortex of the macaque monkey and observed that in some thalamic areas small and large terminals were spatially intermingled and segregated in other areas (the ventral nucleus of the pulvinar). In the dLGN, only small CT terminals were found in dense projection areas and they formed solid stripes. Interestingly, PHA-L injections in area 18 labelled only the small CT terminals in the pulvinar [62] confirming the earlier degeneration studies. In the macaque monkey the projection from the primary visual cortex to dLGN arises from pyramidal

neurons in layer VI, whereas the projection to the pulvinar derives from layer V pyramidal cells [41].

Based on the anterograde transport of biocytin after small iontophoretic injections in the primary visual cortex of the rat, Bourassa and Deschênes [12] were able to reconstruct the axonal projections of small groups of cortical neurons. They distinguished three classes of CT neurons. The pyramidal cells whose cell body resides in the upper part of layer VI project to the RT and the dLGN. In the dLGN, these axons give rise to a dense plexus of terminals, which form a rod oriented in the same direction as the projection of the retinal axons. The pyramidal neurons in the lower part of layer VI project to the RT and participate in the formation of the rod-like projection in the dLGN. However, these axons also project to LP. A third class of CT neuron has its soma in layer V and projects to the pontine nuclei and tectum in addition to its projection to the thalamus. Within the thalamus, these axons do not terminate in the dLGN, but project to the vLGN, LP, and LD. The geometry of the axonal branches forming the terminal plexus in these nuclei is different from that of the layer VI projections to dLGN: the axons bifurcate at larger angles and they do not form rod-like structures. At the light microscopic level, the terminal fields in LP and LD contain large terminals, whereas the terminals in the dLGN are small (see Fig. 2 in [12]). These two types of terminals were compared at the ultrastructural level by Vidnyánszky et al. [83]. These authors not only confirmed the ultrastructural differences between these terminals, but also showed that the postsynaptic elements express different types of metabotropic glutamate receptors. The small terminal in the dLGN establishes a synaptic contact with a dendritic profile that, at the level of the postsynaptic membrane, is immunopositive for mGluR1. The postsynaptic element in LP is immunonegative for this receptor. This observation supports the notion of functional differences between two morphologically distinct synaptic projections that are both glutamatergic.

The two types of CT terminals were also found in a light microscopic analysis of the projections from the primary visual cortex of the cat [53]. The small terminals (ca. 1 μm) in the dLGN form a terminal plexus that crosses all laminae in a perpendicular orientation. The large boutons (about 2 μm) were found in LP where they form clusters 200 μm in diameter. In addition, these authors reported that large terminal boutons were present in the projection from the primary visual cortex to the anterior portion of the pulvinar nucleus and the vLGN, whereas the small boutons characterised the projections to the RT and the perigeniculate nucleus. The laminar origin of these projections was studied earlier with retrograde tracing methods [2,26] and is summarized in Fig. 1.

Feed-back and feed-forward projections. Two functional concepts emerge from these anatomical studies. The projection to the dLGN in the species studied so far is strictly topologically organized and is confined to the part of the principal relay nucleus from which the cortical column receives its thalamic projection. This projection originating from layer VI neurons can therefore be considered to represent a *feed-back* using small CT terminals. The second functional concept relates to the projection to the "higher order nuclei" (LD, LP, and pulvinar). It arises from layer V cells and terminates with large CT boutons. Using this terminal, the primary visual cortex conveys information to secondary visual areas [23], corresponding to a *feed-forward* projection.

The *feed-back* projection to dLGN is generally considered to be functionally important in the modulation of the activation of TC neurons (e.g., [27,37,43]). This is different for the projection from primary visual cortex to higher order thalamic nuclei. In the monkey, Bender [10] demonstrated that the responses of neurons in the pulvinar to visual stimulation disappears after lesion of the visual cortex. The large CT terminals may therefore be responsible for the visual responses in this part of the thalamus, thus playing a key role in pathways re-entering the cerebral cortex from the pulvinar [28].

Somatosensory Cortex

Rodent data. In rodents, CT projections from the primary somatosensory cortex (SI) terminate in RT, the medial and lateral parts of the ventroposterior nucleus (VPM and VPL), as well as the nuclei of the posterior complex (PO). The classic knowledge of these projections was based on anterograde degeneration studies (e.g., [58]) and experiments using the anterograde transport of radioactive labeled amino acids (for the rat; see [57,93]). More recently introduced tract tracing methods allowed the light microscopic study of the morphology of the CT projections and the analysis of their topological organization. We review these studies starting from the work performed on the somatosensory pathway involved in rodents in the processing of information from the whisker follicles.

The ventrobasal nucleus of the thalamus (VB) is the principal thalamic relay processing sensory information from the mystacial whisker follicles. It receives ascending projections from the trigeminal sensory complex in the brainstem and projects to SI. In the VB, the representation of an individual whisker follicle forms a morphological unit visible in Nissl-stained histological sections or with cytochrome-oxidase histochemistry. These units were named "barreloids" [82]. In SI, the representation of each whisker is equally visible in Nissl-stained horizontal sections through layer IV, where the morphological units were named "barrels" [95]. Thalamocortical projections from a barreloid terminate within a single barrel [3,74,90]. This projection forms the morphological basis for the functional one-to-one relationship between each barreloid and each cortical barrel [7,8]. Within SI, whisker stimulation activates a cortical column, that at the level of layer IV comprises a single barrel. These radial units, encompassing all cortical layers, were termed barrel columns.

The iontophoretic application of the anterograde tracer PHA-L in SI of the mouse filled cortical neurons within a barrel column [32]. These injections confirmed the CT projections from SI to the RT, VB, and the medial part of PO (POm). In the RT and VB, the CT projections terminate in a plexus oriented along a rostro-caudal axis. Within such a rod, the labeled terminals are small (ca. 1 μm) and densely packed. The CT projection to POm also terminates in the form of a rostro-caudally oriented rod. However, within the terminal field in POm the CT fibers are less densely packed and form large ("giant") terminals with a diameter of 2–5 μm. Using PHA-L labeling from the murine barrel cortex, the electron microscopic study confirmed the existence of small and giant CT terminals [33]. Both types of terminals form asymmetric synapses. In VB, the postsynaptic elements contacted by the small terminals correspond to small dendritic profiles. The giant terminals in PO appear in Electron Microscope (EM)-material as large profiles filled with synaptic vesicles. Each terminal engulfs several excrescences from a single, proximal dendrite. Within this glomerulus-like arrangement, a single terminal makes several synapses (>5) as well as numerous puncta adhaerentia (up to 15).

In a series of experiments using restricted iontophoretic injections of biocytin, Deschênes and his coworkers demonstrated elegantly the origin of the various CT projections from SI in the rat [11]. The small CT terminals in VB arise from neurons in layer VI, that give collaterals to RT, whereas CT axons originating from layer V terminate with giant boutons that do not give collaterals to the RT, but also terminate in brainstem nuclei (e.g., the pontine nuclei).

Cat and monkey data. A similar pattern of CT projections was described in the somatosensory cortex in the cat [34,58,72]. In this species, SI projects in the thalamus to VPL, VPM, and PO. The ultrastructural features of the projection to VP are represented by small terminals making asymmetric synapses with dendrites outside the synaptic glomerulus [35]. To our knowledge, the morphology of the CT projections to PO has not yet been examined in detail. In the macaque monkey, the morphology of the CT projections from SI was recently described by Darian-Smith and coworkers [17], using biotin dextran amine (BDA) and Lucifer Yellow dextran (LYD) as anterograde tracers. They observed small and large (1.5–2.5 μm) terminals within separate termination areas in the VPL pars caudalis (VPLc) of the macaque after BDA or LYD injections in SI. After LYD injection in cortical area 7a both types of CT terminals were observed in the medial pulvinar. There are no conclusive studies in the monkey demonstrating that the small and giant endings originate from separate CT neurons. However, there is indirect evidence suggesting that the large type of CT terminals arise from layer V of both SI and area 7a, whereas the small terminals originate from layer VI cells [17].

Reciprocity of CT and TC projections in the somatosensory system. In general, CT projections were initially considered to form reciprocal connections with the respective thalamic relay nucleus. However, in the rodent and monkey the part of the thalamic relay nucleus recipient of SI cortical axons was larger than the origin of the TC projection. In the whisker-to-barrel pathway of the mouse, Hoogland et al. [32] demonstrated that a single barrel column gives rise to a cortical projection that terminates in VB within its corresponding barreloid, as well as in neighboring barreloids. The topological organization is such that a single barrel column projects to a set of barreloids that together represent an arc of whisker follicles [32]. A projection that extends beyond strict reciprocal topology was also observed in the whisker-to-barrel pathway of the rat [18]. After cortical injections of a mixture of anterograde and retrograde tracers in the macaque monkey, the extent of the cortical projections from SI was larger than the part of the thalamic nucleus filled with the retrogradely labeled neurons [17]. These examples show that the output of a cortical column influences neuronal processing in the part of the thalamus from which specific sensory information originates, as well as in parts of the thalamus that give rise to projections to neighboring cortical columns.

Motor Cortex

Rat data. The morphology of CT terminals originating from the motor cortex has been established in the rat, using PHA-L as an anterograde tracer [67]. The main projection originating from the face, forelimb, or hindlimb territories of the motor cortex terminated as small endings in the thalamic ventrolateral nucleus (VL) (Fig. 1). The same type of endings was observed for an additional projection, quantitatively smaller, terminating in the VB. Interestingly, a third target region, PO, contained a mixture of small and giant endings. As in the auditory system of the rat, the giant endings in PO originating from the motor cortex had a diameter ranging from 5 to 10 μm.

Cat data. The CT projection originating from the motor cortex of the cat has been investigated with anterograde degeneration [58]. Following lesion of the primary motor area (M1) in the cat, degenerating boutons were observed mainly in VL and a lower number in VB. Additional terminal degeneration was found in the RT, ventral anterior nucleus (VA), central lateral nucleus (CL), central medial nucleus (CM), mediodorsal nucleus (MD) and parafascicular nucleus (Pf) [58]. Using the same tracing technique, Rinvik [58] also described the topography of the CT projection of the secondary motor cortex of the cat (MII), terminating in VL, VB, VA, CM, Pf, CL, and MD. A more precise investigation of the topography and synaptic morphology of the CT projection originating from M1 in the cat was based on BDA tracing data [75]. The target nuclei in the thalamus are RT, VA-VL, CL, and CM (Fig. 1). The densest projection was observed in VA-VL. In accordance to observations in other systems and other mammals, layer VI cortical neurons were seen to give rise to numerous small endings in VA-VL. In contrast, layer V neurons gave rise to smaller clusters of giant terminals in VA-VL. A further distinction was that layer VI neurons send axon collaterals to the RT (small endings), whereas layer V neurons did not project to the RT (Fig. 1).

Monkey data. In the macaque monkey, the precise morphology of the CT projection has been assessed in M1, supplementary (SMA), and dorsal premotor (PMd) cortical areas [68] using BDA as an anterograde tracer. Typical data derived from a comparable tracing experiment are illustrated in Figs. 3 and 4. A representative BDA injection site in M1 is shown in Fig. 3A. Anterogradely labeled terminal fields are present in the ipsilateral thalamus, whose location and extent are illustrated in Fig. 3B for an individual frontal section of the thalamus. The most lateral part of this terminal field is viewed in more details in Fig. 3C, where one can distinguish easily three zones containing giant CT endings (arrows). Giant and small CT endings are shown at higher magnification in Fig. 4 (A and B, respectively). In panel A, the two right insets illustrate a giant ending *terminal* (top) and a giant ending *en passant* (bottom). As summarized in Figs. 1 and 5, SMA and PMd exhibited a similar pattern of CT projection. First, they send a main projection towards the oral part of VL (VLo) formed by small endings. The same type of endings corresponds to the termination of an additional projection to the oral part of VPL (VPLo). Finally, both small and giant endings, originating from SMA and PMd were found in MD. In MD, giant endings were round or ovoid boutons, with a diameter ranging from 2 to 6 μm [68]. In contrast to SMA and PMd, the CT projection originating from M1 does not reach MD. It is directed mainly towards VPLo and VLo, the density and size of the terminal fields being larger in the former than in the latter thalamic nuclei. In both VPLo and VLo, the endings were in general of small size. However, M1 sends a few giant endings to VPLo (Figs. 1 and 5), although their morphology is similar to that observed for the giant endings in MD originating from SMA and PMd. As illustrated in Fig. 5, these giant endings deriving from M1 terminate in the thalamic nucleus providing the major input to M1, thus corresponding to a *feed-back* projection system (Fig. 5). The giant endings in MD originating from SMA and PMd also contribute to a *feed-back* projection system but, in addition, they provide an anatomical support for long distance *feed-forward* projection via MD from SMA to PMd and the prefrontal cortex (Fig. 5).

CT Projection from the Prefrontal Cortex

As a result of a BDA injection in the prefrontal cortex of the rat [49], terminal fields were located mainly in MD, where a dual morphology of endings was found ipsilaterally to the injected hemisphere. A majority of small size endings was observed, mixed with larger size swellings, most likely corresponding to the aforementioned giant endings. The prefrontal cortex also projects to the contralateral MD, but almost exclusively with small endings [49].

In the macaque monkey, the CT projection originating from the prefrontal cortex was analyzed with respect to topography based on injection of radio-labeled amino acids [78]. The main target nucleus was MD, where the topography of axon terminal fields varied depending on the location of the tracer injection in the

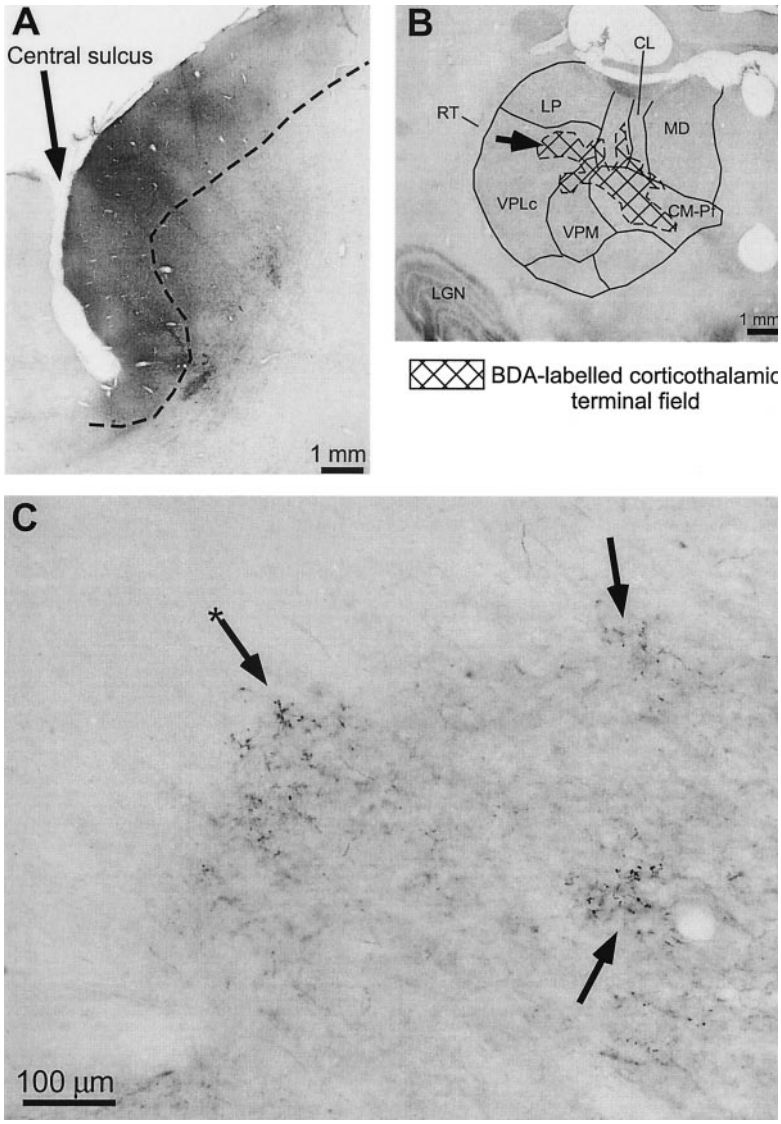

FIG. 3. Original tracing data derived from an experiment in which the tracer biotinylated dextran amine (BDA) was injected in primary motor cortical area (M1) in a macaque monkey. (A) Photomicrograph of a frontal section of the left hemisphere, centered on the central sulcus and its rostral bank, corresponding to the hand representation in M1. The dashed line represents the border between the gray and the white matter. The dark spot corresponds to the BDA injection site extending from the fundus of the central sulcus up to the top of the rostral bank of the central sulcus. (B) Low magnification photomicrograph of a Nissl-stained frontal section of the thalamus, with delineation of the principal nuclei. The hatched territory delineated with a dashed line corresponds to the terminal fields labeled as a result of the BDA injection in M1 and transposed from the adjacent section. The most lateral part of the BDA-labeled terminal field (arrow) is shown in (C) at higher magnification. Within the terminal field, three clusters of giant endings can be distinguished (arrows). A portion of the cluster denoted by the arrow with the asterisk is represented at high magnification in Fig. 4. Abbreviations: CL, central lateral nucleus; CM-Pf, Central–Parafasicular nuclei; LGN, lateral geniculate nucleus; LP, lateral posterior nucleus of thalamus; MD, mediodorsal nucleus; VPLc, ventroposterolateral nucleus, oral part; VPM, ventroposteromedial nucleus.

prefrontal cortex [78]. However, the morphology of CT endings in MD could not be visualized by autoradiography [78]. Using the same anterograde tracing technique combined with electron microscopy, another study addressed the issue of the morphology of CT terminals originating from the dorsal bank of the principal sulcus in the macaque monkey [73]. In MD, the endings were divided into two categories based on their size: the majority of endings were small, whereas the second type of endings were large and less numerous. This duality is likely to correspond to the two types of CT endings described above, which derive from the

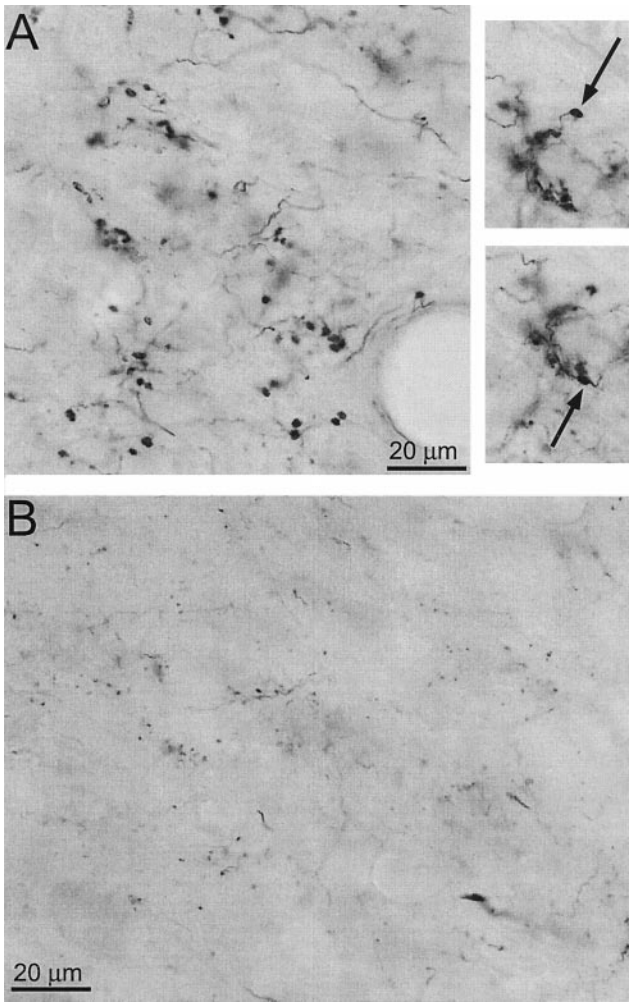

FIG. 4. High magnification view of giant corticothalamic (CT) endings in ventroposterolateral nucleus, caudal part (VPLc) labeled with a biotinylated dextran amine (BDA) injection in primary motor cortical area (M1) (A). The two insets at the right illustrate a giant ending terminal (top) and a giant ending en passant (bottom). For comparison, (B) illustrates another portion of the same terminal field in VPLc, where only small CT endings are present.

auditory, visual, somatosensory, and motor cortices. The small and large CT endings observed in MD [73] may originate in the prefrontal cortex from two distinct types of CT neurons [25,96]: numerous neurons located in layer VI and fewer neurons in layer Vb, respectively. Such a laminar arrangement of CT neurons in the prefrontal cortex, possibly giving rise to two distinct types of terminals (small and large), is reminiscent of the small and giant endings originating from the auditory, motor, somatosensory, and visual cortices (see for example, [11,12,17,23,33,42,51,62,75]).

CT Projection From Other Cortical Areas

Two types of CT endings, based on size and morphology, were found in the rat as a result of injections of WGA-HRP in the presubiculum [50]: small and medium-sized endings were seen in the anterodorsal and anteroventral thalamic nuclei. In contrast, after injection in the posterior cingulate cortex, only small-sized endings were observed [50]. In the rat, using the anterograde degeneration tracing technique combined with electron microscopy, it was found that the piriform cortex sends a projection to MD with two types of terminals [39]. The terminals consisted of small and large endings, which preferentially established synapses on the distal or proximal dendrites, respectively.

COMMON ORGANIZATION OF THE CT PROJECTION ACROSS SPECIES AND SYSTEMS

Laminar Origin of the CT Projection

Based on several studies, the laminar origin of the CT neurons appears to dictate the morphology of the terminals in the thalamus (see [25,73] for the prefrontal cortex in macaque monkeys; see [51] for the primary auditory cortex of the cat; see [75] for the motor cortex of the cat; see [11] for SI in the rat; see [17] for the somatosensory cortex of the macaque monkey; see [12] for the primary visual cortex of the rat). Neurons in layer VI give rise exclusively to small endings whereas neurons in layer V (less numerous) send axons terminating with giant (large) endings. Both boutons *en passant* or *terminaux* were observed for small and giant endings (see Fig. 4A for giant endings). However, whether layer V neurons give rise exclusively to giant endings remains a matter of debate. In the motor and auditory systems, we observed that the same axons are the source of giant and small endings [9,66–68]. Similarly, in the visual system, Rockland [61,62] reported that "small and large profiles are intermixed on a single arbor. . . ." The latter observations support the idea that layer V neurons do not give rise to giant endings exclusively, but most likely also to small endings.

Topographical Organization of the CT Projection

The present review suggests that virtually all cortical areas investigated so far give rise to a dual pattern of projection, corresponding to the terminal fields formed by small and giant endings. The axons giving rise to small endings and originating from layer VI neurons form relatively large and continuous terminal fields, whereas territories with giant endings are more restricted and often appear as a mosaic of small patches. After an injection of an anterograde tracer in the cerebral cortex, the total area of labeling corresponding to small endings is by far larger than territories containing giant endings. Within individual sections, the area of terminal fields with small endings often is 10 or even 20 times the area of terminals formed by giant endings (e.g., [68]). Consequently, the CT small endings dramatically outnumber the CT giant endings.

With respect to precise topography, there is some variability across systems and species (Table 1). Basically, two main patterns of arrangement can be distinguished (Fig. 6):

1. The giant endings are located in a thalamic nucleus distinct from that receiving the principal projection formed by small endings (Fig. 6, left panel). Such an arrangement was observed for the motor cortex of the rat where giant endings were located in PO, segregated from the main terminal field in VL [67]. The same separated pattern of arrangement was observed in the macaque monkey for the CT projections of the motor cortical areas SMA and PMd that terminate mainly in VLo, whereas giant endings are found in MD [68] (Fig. 5). The auditory CT projection originating from tonotopically organized cortical areas also belongs to this first pattern, both in the rat [66] and in the cat [9] (Fig. 2). The same holds true for the CT projection originating from the visual cortex of the three species and for the CT projection from SI in the rat and in the cat (Table 1).
2. The giant endings are located in the principal target nucleus of the CT projection, i.e., in the thalamic nucleus where the small

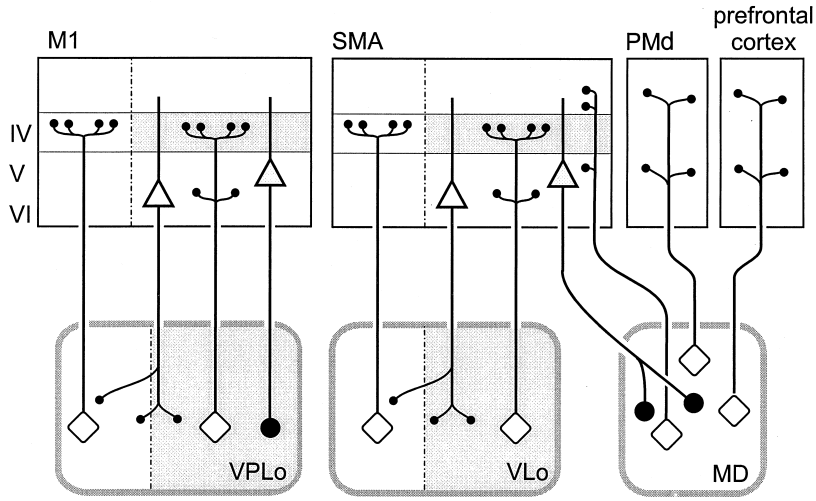

FIG. 5. The organization and morphology of the corticothalamic (CT) projection originating from primary motor cortical area (M1) and supplementary motor cortical area (SMA) in macaque monkeys. Black rectangles are for cortical areas whereas boxes in gray are for thalamic nuclei. CT neurons are represented by open triangles whereas thalamocortical (TC) neurons appear as open diamonds. Axon terminals are represented by filled circles (small and large). The cortical layers IV, V, and VI are indicated. As a result of a tracer injection in M1 or in SMA (gray zone in the top two rectangles representing M1 and SMA), anterogradely labeled terminals (filled circles) and retrogradely labeled TC neurons (open diamonds) are found in the thalamic nuclei ventral lateral nucleus, oral part (VLo), ventroposterolateral nucleus, oral part (VPLo), and mediodorsal nucleus (MD) (see [68]). For simplification, the labeling observed in VLo after an injection in M1 and in VPLo after an injection in SMA (both corresponding to small endings, see Fig. 1) is not represented. Although the two territories of labeling (anterograde and retrograde) largely overlap, there are zones of mismatch (see text). The main CT projection from M1 or SMA terminating with small endings may contact TC neurons in the zone of reciprocity in VPLo or VLo, respectively (gray area). The injected cortical zone thus receives ascending information from TC neurons and the latter neurons then may receive *feed-back* inputs from the layer VI neurons located in the zone of cortex where they project. In contrast, some layer VI neurons may send a CT projection to a zone of non-reciprocity (white zone in VPLo or VLo), where TC neurons may then relay the information coming from the cortex back up to a neighboring cortical zone. This cortico-thalamo-cortical loop corresponds to a "local" feed-forward projection system (see text). Another *feed-forward* projection system (at "long distance") is illustrated. The cortico-thalamo-cortical loop originates in layer V of the SMA, where neurons send a CT projection formed by giant endings in MD [68]. The terminal zone in MD is superimposed with clusters of TC neurons projecting to the areas dorsal premotor cortex (PMd) and to the prefrontal cortex [69]. This cortico-thalamo-cortical loop thus allows a given cortical area (e.g., SMA) to transfer indirectly, but rapidly, information to a distant area (PMd or prefrontal cortex), in parallel to the direct cortico-cortical projections (not represented here). Although not represented here, a similar cortico-thalamo-cortical loop involving giant endings allows PMd to send rapid information to SMA and to the prefrontal cortex [69].

endings form the largest and densest clusters of terminals (Fig. 6, right panel). This is the case in the cat for the projection originating from the motor cortex and terminating in VA-VL [75], in the macaque monkey for the projection from M1 to VPLo (Fig. 5), and from SI to VPLc [17]. In the auditory system, this second pattern of arrangement was observed for the CT projection originating from AII in the cat.

The organization of the different cortical areas across systems and species with respect to these two patterns of CT terminal arrangement is summarized in Table 1. In the auditory and visual systems, the pattern of arrangement of CT terminals remains constant across species. On the contrary, for SI and M1, a progressive change seems to occur from rat to monkey (Table 1). For the non-primary motor and somatosensory cortices, the data available are not sufficiently complete to draw a conclusion about the variation of the CT projection pattern across species (Table 1).

With the exception of the prefrontal cortex [49], data are available only for the CT projection terminating in the ipsilateral thalamus. It is known that the CT projection originating from the frontal cortex also includes a component terminating in the contralateral thalamus (e.g., [14,47]), which is less dense than the ipsilateral component. The fine morphology of the terminals in the contralateral thalamus has not been established in detail, and whether giant endings are present contralaterally remains an open question.

RECIPROCITY OF THE CT AND TC PROJECTIONS

Does the location of CT terminal fields strictly overlap the clusters of TC neurons projecting to the zone of cortex from which the CT projection originates? In general, most studies report that the two systems of projections largely overlap in the thalamus, thus implying that the territories formed by CT endings generally match

TABLE 1
PATTERN OF ARRANGEMENT OF THE CORTICO-THALAMO-CORTICAL LOOPS

	Rat/Mouse	Cat	Monkey
Auditory			
A1 (AAF-PAF)	1	1	1 (?)
AII (Belt)	2 (?)	2	2 (?)
Visual			
Area 17	1	1	1
Somatosensory			
S1	1	1	2
Area 7a	–	–	2
Motor			
M1	1	2 (1)	2
SMA	–	–	1
PMd	–	–	1

A1, primary auditory cortical field; AAF, anterior auditory cortical field; PAF, posterior auditory cortical field; AII, secondary auditory cortical field; S1, primary somatosensory cortex; M1, primary motor cortical area; SMA, supplementary motor cortical area; PMd, dorsal premotor cortex.

Patterns 1 and 2 refer to the two arrangements represented in Fig. 6. In pattern 1, the corticothalamic projection giving rise to giant endings terminates in a thalamic nucleus distinct from that receiving the major corticothalamic projection formed by small endings. As a consequence, the giant ending projection represents an anatomical basis for *long distance feed-forward* transfer of information (see text). In pattern 2, the cortico-thalamic projection giving rise to giant endings terminates in the same thalamic nucleus as that receiving the major corticothalamic projection formed by small endings. As a consequence, the corticothalamic projection consists mainly of a *feed-back* and *local feed-forward* transfer of information (see text).

the clusters of TC neurons. However, more detailed observations provided evidence of some mismatch, although non-overlapping territories are spatially relatively restricted. Spatial mismatch was observed in the projection to MGB originating from the auditory cortex of the rat [91]. Combining HRP as a retrograde tracer and autoradiography for anterograde tracing, Winer and Larue [91] found that there was a "gross congruence of TC and CT projections, but zones containing many HRP-labeled neurons were not completely coextensive with areas of heavy terminal labeling in the MGB". The same authors observed that "the autoradiographic zones of non-reciprocity are more extensive than were the retrograde zones of non-reciprocity" [91]. As indicated by Winer and Larue themselves [91], there are technical limitations to the interpretation of the reciprocity data. First, the injection sites of the tracers used are difficult to define accurately. Second, it was not possible to examine the retrograde and anterograde labeling within the same section. In the auditory system, a non-strict reciprocity of the TC and CT projections has also been observed for the dorsal zone of the auditory cortex of the cat [31].

Evidence for non-reciprocity was found in VPLc and in the pulvinar for the projections from SI (areas 1 and 3) and area 7a of the macaque monkey, respectively [17]. Similarly, as a result of BDA injections M1, SMA, or PMd of macaque monkeys, we also observed a mismatch in the thalamus between retrograde and anterograde labeling [68]. CT terminals were located in thalamic territories devoid of labeled TC neurons, and clusters of TC neurons not in register with CT terminal fields were found (Fig. 3). However, thalamic zones corresponding to such spatial mismatches were more restricted than matching zones. In line with the findings of Winer and Larue [91] in the MGB, we observed in the motor thalamus that non-reciprocal zones of CT terminal fields were larger than non-reciprocal clusters of TC neurons [68]. The comparison of the anterograde and retrograde labeling resulting from the same tracer injection in the cortex may be problematic and therefore observations of mismatch are questionable [68]. However, more convincing evidence for mismatch has been provided by using a cocktail of an anterograde tracer mixed with a retrograde tracer. This procedure was performed in the auditory cortex [91] and in the parietal cortex [17]. These mixed injections demonstrated that the anterograde and retrograde territories of labeling largely overlapped, but were accompanied by small zones of labeling not in register.

The analysis of Deschênes and collaborators [18] of the projection from SI of the rat provided the most detailed picture on the topological relationship between the CT and TC projections. The pyramidal cell bodies in the upper part of layer VI project in a strictly reciprocal manner to VPM. In other words, this projection connects a single barrel column in SI with its appropriate barreloid in the thalamus. The pyramidal cells in the lower part of layer VI, however, project not only to the corresponding barreloid but also to neighboring barreloids. This non-reciprocal organization of a subset of the CT projection forms one of the arguments in the formulation of the rule of parity underlying the CT topologic relationship in the somatosensory system of rodents [18]. This rule is in harmony with earlier observations (Fig. 11 in [32]). The functional implications of such mismatches are discussed below.

FUNCTIONAL IMPLICATIONS

Feed-Back *and* Feed-Forward *CT Projections*

The small CT endings, terminating mainly on distal dendrites of thalamic relay neurons, are far more numerous than the large endings that terminate on proximal dendrites and correspond to the sensory ascending inputs, (see [45] for review). Although most CT small endings terminate on distal dendrites, they can exert an influence on the soma comparable to that produced by the proximal and large sensory ascending endings [45]. Similar to the cortico-cortical connections (both intra-hemispheric and callosal), the layer VI CT neurons giving rise to small endings are characterized by long and variable axonal conduction delays, up to 40 ms [45]. In spite of such long delays and temporal dispersion, it has been suggested that the CT neurons have a precise temporal definition. On this basis, Miller [45] proposed that the layer VI CT neurons may contribute to establish *synfire chains*, defined as organized sequences of action potentials, spread across many cells and exhibiting precise temporal structure (e.g., [1,84]).

Another possible role of the CT projection originating from layer VI is to provide an indirect (cortico-thalamo-cortical) pathway to interconnect two cortical loci in a more secure way (high *amplification synaptic factor*) than direct cortico-cortical projections [45]. In other words, the gain is believed to be greater along a cortico-thalamo-cortical loop than along a direct or multi-synaptic cortico-cortical connection [45]. The possibility of such an indirect connection between different cortical loci via a cortico-thalamo-cortical loop is supported by the notion that the CT and TC projection systems do not strictly overlap. Therefore, the spatial mismatch in the thalamus represents an indirect way for a cortical territory to influence a surrounding cortical zone, as proposed by Darian-Smith et al. [17] (see "local" *feed-forward* projections in Figs. 2 and 5). Besides their obvious role as a *feed-back* control system, these considerations imply that the layer VI CT projection system can also contribute to a *feed-forward* projection via the thalamus. However, the mismatch between CT terminal fields and clusters of TC neurons remains relatively small as compared to the overlap (reciprocity) of these two territories. This

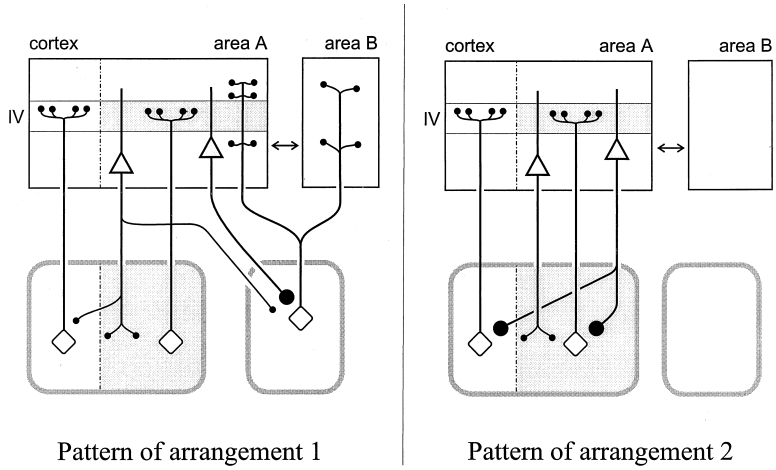

FIG. 6. Schematic representation of the two patterns of giant terminal fields in the thalamus across species and systems (see also Table 1). Black rectangles are for cortical areas whereas boxes in gray are for thalamic nuclei. Open triangles and diamonds represent corticothalamic (CT) and thalamocortical (TC) neurons, respectively. Axon terminals are represented by filled circles. The dashed lines correspond to the border of a column in the cortical area A and to the corresponding thalamic rod. Same conventions as in Figs. 2 and 5. In the first pattern (left panel), a column in a cortical area A receives ascending TC inputs from the corresponding thalamic rod (TC neuron in the gray zone). The same cortical column (layer VI neurons) sends a CT projection terminating with small endings in the corresponding thalamic rod (gray zone of matching of TC and CT projections), as well as in a zone adjacent to the thalamic rod (zone of non-matching). Furthermore, the cortical column also sends a projection with small endings to a second thalamic nucleus, where giant endings are also observed, and originate from layer V neurons of the same cortical column. The giant endings may thus contact TC neurons in this second thalamic nucleus, that in turn project to another cortical area (B). This circuit represents the anatomical support for a "distant" feed-forward projection via a rapid and secure cortico-thalamo-cortical loop (see text). Pattern 1 is also illustrated for the primary (A1), anterior (AAF), and posterior (PAF) auditory cortical areas in Fig. 2, as well as for the supplementary motor cortical area (SMA) and dorsal premotor cortex (PMd) in Fig. 5. In pattern 2 (right panel), the main difference is that giant endings are located in the same nucleus of the thalamus where the small endings form the main CT terminal field in the corresponding thalamic rod. As observed for primary motor cortical area (M1) and primary somatosensory cortex (SI) in monkeys, giant endings tend to be located at the periphery of the main terminal field, thus representing a possible support for a "local" *feed-forward* projection to the same cortical area A, in the zone adjacent to the cortical column (see text).

predominant trend for reciprocity suggests that the CT projection formed by small endings (originating in layer VI neurons) remains a *feed-back* projection system rather than a local *feed-forward* projection. *Feed-back* and local *feed-forward* projection systems involving small CT endings are illustrated schematically in Fig. 2 for the auditory cortex and in Fig. 5 for the motor cortex.

The role of the CT projection originating from layer V neurons is most likely different, since their axonal conduction delay is significantly shorter [45]. Furthermore, the topographical distribution of the giant endings is such that the layer V CT projection system can interconnect rapidly, in a *feed-forward* mode, remote cortical regions (Figs. 2 and 5): "distant" *feed-forward* projections. For example, in the auditory system of the cat (Fig. 2), the tonotopic cortical areas AI, AAF, and PAF project indirectly to the secondary auditory cortex AII via the dMGB (Fig. 2; see also [9]). Similarly, in the motor system of primates, rapid interconnections between SMA and PMd are possible via the CT projection terminating with giant endings in MD. The same is true for a rapid projection from SMA and PMd towards the prefrontal cortex, again via the giant endings in MD (Fig. 5) [68,69]. A further topographical distinction between layers V and VI neurons giving rise to a CT projection is that layer VI neurons send axon collaterals to the RT, whereas this is not the case for the axons of layer V neurons [11,28,75].

In conclusion, topographic and reciprocal properties of the two CT projection systems suggest that the projection with small endings may participate in *feed-back* control and, to a lesser extent, to a local *feed-forward* transfer of information (Figs. 2 and 5). The CT projection terminating with giant endings can also participate in *feed-back* control and a "local" *feed-forward* connection. However, giant endings may be more prominently engaged in "distant" and rapid *feed-forward* transfer of information, even between distinct and remote cortical areas. The transfer of information through giant endings is likely to be very secure as one might expect from large presynaptic terminals. Secure transmission was demonstrated in the cochlear nucleus and superior olivary complex for large endings such as the endbulbs and calyces of Held [29]. When an action potential reaches the presynaptic element, it has a very high probability of generating an action potential in the postsynaptic cell, with fine preservation of temporal precision of firing [13,29].

Considering the duality of CT endings, Guillery [28] catego-

rized as *first order nuclei*, thalamic nuclei receiving primary afferent fibers from the periphery and CT inputs from layer VI neurons. In *first order nuclei*, the CT projection is acting essentially as a thalamic gate, allowing the cortex to modulate the inputs it receives from the thalamus [28]. In contrast, *high order nuclei* in the thalamus mostly receive inputs from layer V neurons in cortex. In this second category, Guillery [28] included thalamic nuclei such as MD, pulvinar, and PO; consistent with observations that giant endings are indeed located in such nuclei after the injection of an anterograde tracer in SMA, PMd, and area 7a in monkeys [17,68]. However, this distinction between *first order and high order* thalamic nuclei should not be taken strictly [28], considering for example that the nucleus VPLc receives ascending inputs from the periphery and also CT giant endings from SI. Similarly, in the auditory thalamus, the dMGB is the main thalamic target of layer V neurons giving rise to giant endings, but the dMGB also receives inputs from the dorsal cortex of the inferior colliculus [6,64].

Effects Exerted by CT Projections

Several studies have addressed the question of the influence exerted by the CT projection on the properties of thalamic neurons, without however distinguishing the two systems of projections (small and giant endings). In the auditory system, the influence of the CT projection on thalamic neurons was investigated indirectly by transiently inactivating (by cooling) AI [54,70,85,86]. Inactivation of AI had an effect on a vast majority of neurons recorded from the MGB, particularly when a wide range of discharge properties were considered [85]. Among multiple effects, inactivating AI could substantially modify the tuning properties of MGB neurons [85]. More generally, inactivating AI induced a large variety of complex effects on the discharge properties of MGB neurons, with a large variability from one unit to another, and across MGB subdivisions [70,85]. This variability of effects most likely reflects that the corticofugal influence can be mediated either by direct projections on MGB relay neurons or by indirect projections on MGB interneurons. Another, even more indirect cortical influence can be mediated by projections to the RT, which also receives inputs from AI and projects either to relay neurons or interneurons in the MGB. However, a global inactivation of AI may be too crude to assess the properties of the CT projection. A more precise approach has been undertaken more recently where an electric stimulus was delivered focally in AI in a locus in register with the best frequency of the MGB neuron from which electrophysiological activity was recorded [30]. The vast majority (88%) of MGB units were affected by electrical stimulation of AI [30]. When the modulation of the onset response of MGB units to pure tones was assessed [30], the cortical effect was more often facilitatory (2/3 of units) than inhibitory (1/3 of units). The cortical modulation of MGB units was found to depend on the intensity of AI stimulation as well as the temporal relationship between the electrical shock and the tone. Furthermore, the effect depended strongly on the precise locus in AI where the electrical stimulus was delivered. The maximal effect was observed when the electric stimulus was delivered in the iso-frequency contour corresponding to the best frequency of the MGB unit. Electric stimulation of neighboring iso-frequency contours evoked smaller effects or no effect at all. Within the iso-frequency contour in AI corresponding to the best frequency of the MGB unit, the precise topography of the corticofugal modulatory effects was patchy, in the form of spots where the stimulus was effective and spots where no effect was obtained [30]. These patches had an average diameter of about 1.1 mm, in line with the size of patches formed by the terminal fields of the CT projection in vMGB [30].

The details of the mechanisms underlying the influence of the cortex on the activity within the thalamus were investigated in the visual system with intracellular recordings of LGN neurons in response to electric stimulation of the CT system [44]. CT activation induced a prolonged EPSP (lasting up to several seconds) in LGN relay neurons, due to a decrease of the membrane conductance for potassium in the cells [44]. These data were interpreted in the sense that the long and slow EPSP due to cortical stimulation produces a switch from a burst firing mode to a single spike activity mode, occurring in parallel with enhanced sensory transmission and arousal [44].

In the somatosensory system, the whisker-to-barrel pathway of the rat revealed a principle that may well apply to none-whisker information processing parts of the mammalian thalamus. In general, CT projections are considered to be of importance in modifying the relay of sensory information towards the cerebral cortex. In a study of the influence of the cortical projections from SI on the response properties of neurons in VB and POm in the anaesthetized rat, Diamond et al. [22] showed that blocking cortical activity may increase the response to whisker stimulation of VB neurons, whereas POm neurons stop responding to the peripheral stimulus. Taken together with the two types of CT terminals, these observations may indicate that the small endings in VB exert a modulating role in thalamic transmission of sensory information, whereas the giant terminals in PO serve to convey sensory information from the cortex, via this thalamic nucleus, to other cortical areas [33]. In other words, the projection to VB has a typical *feed-back* feature, while the projection to POm appears to be part of a *feed-forward* circuit [89]. It is of interest that these two different functional modes in brain connectivity use two distinct types of axonal connectivity.

In addition to the temporal role possibly played by the CT projection in *synfire chains* discussed above [45], another role in the temporal domain was proposed by Steriade and collaborators [15,16,19,20,79,80]. These authors provided evidence that the synchronization of spontaneous oscillations (fast or slow depending on the level of vigilance) in the thalamus is under the control of the CT *feed-back* volleys. Thalamic oscillators are thus under a powerful synchronizing action of the CT projection which involves predominantly a corticofugal loop exerting its effect via RT [19]. Along similar lines, it was found that the *feedback* CT projection coming from the visual cortex can induce correlated firing in relay dLGN cells carrying information about particular visual features [77]. As a result, the efficiency of the relay cells to drive the visual cortex will increase and will contribute to lock the ensemble of driven neurons to the stimulus [77].

The CT projection also contributes to establish the properties of receptive fields of thalamic neurons, for instance in LGN [76] and VPM [38]. Lesion [38] induced plasticity in the thalamus depends, at least in part, on the CT projection originating from SI. Following peripheral deafferentation, the resulting reorganization of the receptive field of thalamic neurons was diminished when SI was reversibly inactivated by cooling [38].

Future electrophysiological investigations are needed to differentiate the effects of the CT projections originating from layer VI or layer V neurons. This will require stimulation or inhibition of one or the other cortical layer. One difficulty with this approach will be to record from thalamic neurons influenced by giant endings, because they form very small clusters of terminals that will be difficult to localize *in vivo*. Nevertheless, relevant data may be collected by matching a posteriori the precise location of a physiologically characterized unit in the thalamus with the distribution of CT terminal fields established in the same animal using neuroanatomical tracing experiments.

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REFERENCES

1. Abeles, M. Local cortical circuits. In: Studies of brain function. Berlin/Heidelberg: Springer Verlag; 1982:102.
2. Abramson, B. P.; Chalupa, L. M. The laminar distribution of cortical connections with the tecto- and cortico-recipient zones in the cat's lateral posterior nucleus. Neuroscience 15:81–95; 1985.
3. Agmon, A.; Yang, L. T.; O'Dowd, D. K.; Jones, E. G. Organized growth of thalamocortical axons from the deep tier of terminations into layer IV of developing mouse barrel cortex. J. Neurosci. 13:5365–5382; 1993.
4. Andersen, R. A.; Knight, P. L.; Merzenich, M. M. The thalamocortical and corticothalamic connections of AI, AII, and the anterior auditory field (AAF) in the cat: Evidence for two largely segregated systems of connections. J. Comp. Neurol. 194:663–701; 1980.
5. Andersen, R. A.; Snyder, R. L.; Merzenich, M. M. The topographic organization of corticocollicular projections from physiologically identified loci in the AI, AII, and anterior auditory cortical fields of the cat. J. Comp. Neurol. 191:479–494; 1980.
6. Andersen, R. A.; Roth, G. L.; Aitkin, L. M.; Merzenich, M. M. The efferent projections of the central nucleus and the pericentral nucleus of the inferior colliculus in the cat. J. Comp. Neurol. 194:649–662; 1980.
7. Armstrong-James, M.; Callahan, C. A.; Friedman, M. A. Thalamocortical processing of vibrissal information in the rat. I. Intracortical origins of surround but not centre-receptive fields of layer IV neurones in the rat S1 barrel field cortex. J. Comp. Neurol. 303:193–210; 1991.
8. Armstrong-James, M.; Callahan, C. A. Thalamo-cortical processing of vibrissal information in the rat. II. Spatiotemporal convergence in the thalamic ventroposterior medial nucleus (VPm) and its relevance to generation of receptive fields of S1 cortical "barrel" neurones. J. Comp. Neurol. 303:211–224; 1991.
9. Bajo, V. M.; Rouiller, E. M.; Welker, E.; Clarke, S.; Villa, A. E. P.; de Ribaupierre, Y.; de Ribaupierre, F. Morphology and spatial distribution of corticothalamic terminals originating from the cat auditory cortex. Hear. Res. 83:161–174; 1995.
10. Bender, D. B. Visual activation of neurons in the primate pulvinar depends on cortex but not colliculus. Brain Res. 279:258–261; 1983.
11. Bourassa, J.; Pinault, D.; Deschênes, M. Corticothalamic projections from the cortical barrel field to the somatosensory thalamus in rats: A single-fibre study using biocytin as an anterograde tracer. Eur. J. Neurosci. 7:19–30; 1995.
12. Bourassa, J.; Deschênes, M. Corticothalamic projections from the primary visual cortex in rats: A single fiber study using biocytin as an anterograde tracer. Neuroscience 66:253–263; 1995.
13. Bourk, T. R. Electrical responses of neural units in the anteroventral cochlear nucleus of the cat. Doctoral thesis, Massachusetts Institute of Technology, Cambridge, MA; 1976.
14. Carretta, D.; Sbriccoli, A.; Santarelli, M.; Pinto, F.; Granato, A.; Minciacchi, D. Crossed thalamo-cortical and cortico-thalamic projections in adult mice. Neurosci. Lett. 204:69–72; 1996.
15. Contreras, D.; Destexhe, A.; Sejnowski, T. J.; Steriade, M. Control of spatiotemporal coherence of a thalamic oscillation by corticothalamic feedback. Science 274:771–774; 1996.
16. Contreras, D.; Steriade, M. Spindle oscillation in cats: The role of corticothalamic feedback in a thalamically generated rhythm. J. Physiol. 490:159–179; 1996.
17. Darian-Smith, C.; Tan, A.; Edwards, S. Comparing thalamocortical and corticothalamic microstructure and spatial reciprocity in the macaque ventral posterolateral nucleus (VPLc) and medial pulvinar. J. Comp. Neurol. 410:211–234; 1999.
18. Deschênes, M.; Veinante, P.; Zhang, Z. W. The organization of corticothalamic projections: Reciprocity versus parity. Brain Res. Rev. 28:286–308; 1998.
19. Destexhe, A.; Contreras, D.; Steriade, M. Mechanisms underlying the synchronizing action of corticothalamic feedback through inhibition of thalamic relay cells. J. Neurophysiol. 79:999–1016; 1998.
20. Destexhe, A.; Contreras, D.; Steriade, M. Cortically-induced coherence of a thalamic-generated oscillation. Neuroscience 92:427–443; 1999.
21. Diamond, I. T.; Jones, E. G.; Powell, T. P. S. The projection of the auditory cortex upon the diencephalon and brainstem in the cat. Brain Res. 15:305–340; 1969.
22. Diamond, M. E.; Armstrong-James, M.; Budway, M. J.; Ebner, F. F. 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. 319:66–84; 1992.
23. Feig, S.; Harting, J. K. Corticocortical communication via the thalamus: Ultrastructural studies of corticothalamic projections from area 17 to the lateral posterior nucleus of the cat and inferior pulvinar nucleus of the owl monkey. J. Comp. Neurol. 395:281–295; 1998.
24. Feliciano, M.; Saldaña, E.; Mugnaini, E. Direct projection from the rat primary auditory neocortex to the nucleus sagulum, paralemniscal regions, superior olivary complex and cochlear nuclei. Aud. Neurosci. 1:287–308; 1995.
25. Giguere, M.; Goldman-Rakic, P. S. Mediodorsal nucleus: Areal, laminar, and tangential distribution of afferents and efferents in the frontal lobe of rhesus monkeys. J. Comp. Neurol. 277:195–213; 1988.
26. Gilbert, C. D.; Kelly, J. P. The projections of cells in different layers of the cat's visual cortex. J. Comp. Neurol. 163:81–105; 1975.
27. Guido, W.; Lu, S. M. Cellular bases for the control of retinogeniculate signal transmission. Int. J. Neurosci. 80:41–63; 1995.
28. Guillery, R. W. Anatomical evidence concerning the role of the thalamus in corticocortical communication: A brief review. J. Anat. 187:583–592; 1995.
29. Guinan, J. J. Jr.; Li, R. Y.-S. Signal processing in brainstem auditory neurons which receive giant endings (calyces of Held) in the medial nucleus of the trapezoid body of the cat. Hear. Res. 49:321–334; 1990.
30. He, J. F. Modulatory effects of regional cortical activation on the onset responses of the cat medial geniculate neurons. J. Neurophysiol. 77: 896–908; 1997.
31. He, J. F.; Hashikawa, T. Connections of the dorsal zone of cat auditory cortex. J. Comp. Neurol. 400:334–348; 1998.
32. Hoogland, P. V.; Welker, E.; van der Loos, H. Organization of the projections from barrel cortex to thalamus in mice studied with Phaseolus Vulgaris-Leucoagglutinin and HRP. Exp. Brain Res. 68:73–87; 1987.
33. Hoogland, P. V.; Wouterlood, F. G.; Welker, E.; van der Loos, H. Ultrastructure of giant and small thalamic terminals of cortical origin: A study of the projections from the barrel cortex in mice using *Phaseolus vulgaris* leuco-agglutinin (PHA-L). Exp. Brain Res. 87: 159–172; 1991.
34. Jones, E. G.; Powell, T. P. The projection of the somatic sensory cortex upon the thalamus in the cat. Brain Res. 10:369–391; 1968.
35. Jones, E. G.; Powell, T. P. An electron microscopic study of the mode of termination of cortico- thalamic fibres within the sensory relay nuclei of the thalamus. Proc. R. Soc. Lond. B Biol. Sci. 172:173–185; 1969.
36. Kelly, J. B.; Wong, D. Laminar connections of the cat's auditory cortex. Brain Res. 212:1–15; 1981.
37. Koch, C. The action of the corticofugal pathway on sensory thalamic nuclei: A hypothesis. Neuroscience 23:399–406; 1987.
38. Krupa, D. J.; Ghazanfar, A. A.; Nicolelis, M. A. L. Immediate thalamic sensory plasticity depends on corticothalamic feedback. Proc. Natl. Acad. Sci. USA 96:8200–8205; 1999.
39. Kuroda, M.; Murakami, K.; Kishi, K.; Price, J. L. Distribution of the piriform cortical terminals to cells in the central segment of the mediodorsal thalamic nucleus of the rat. Brain Res. 595:159–163; 1992.
40. Liu, X. B.; Honda, C. N.; Jones, E. G. Distribution of four types of synapse on physiologically identified relay neurons in the ventral posterior thalamic nucleus of the cat. J. Comp. Neurol. 352:69–91; 1995.
41. Lund, J. S.; Lund, R. D.; Hendrickson, A. E.; Bunt, A. H.; Fuchs, A. F. The origin of efferent pathways from the primary visual cortex, area

17, of the macaque monkey as shown by retrograde transport of horseradish peroxidase. J. Comp. Neurol. 164:287–303; 1975.
42. Mathers, L. H. The synaptic organization of the cortical projection to the pulvinar of the squirrel monkey. J. Comp. Neurol. 146:43–60; 1972.
43. McCormick, D. A.; Bal, T. Sensory gating mechanisms of the thalamus. Curr. Opin. Neurobiol. 4:550–556; 1994.
44. McCormick, D. A.; Von Krosigk, M. Corticothalamic activation modulates thalamic firing through glutamate "metabotropic" receptors. Proc. Natl. Acad. Sci. USA 89:2774–2778; 1992.
45. Miller, R. Cortico-thalamic interplay and the security of operation of neural assemblies and temporal chains in the cerebral cortex. Biol. Cybern. 75:263–275; 1996.
46. Mitani, A.; Shimokouchi, M.; Nomura, S. Effects of stimulation of the primary auditory cortex upon colliculogeniculate neurons in the inferior colliculus of the cat. Neurosci. Lett. 42:185–189; 1983.
47. Molinari, M.; Minciacchi, D.; Bentivoglio, M.; Macchi, G. Efferent fibers from the motor cortex terminate bilaterally in the thalamus of rats and cats. Brain Res. 57:305–312; 1985.
48. Montero, V. M. A quantitative study of synaptic contacts on interneurons and relay cells of the cat lateral geniculate nucleus. Exp. Brain Res. 86:257–270; 1991.
49. Négyessy, L.; Hámori, J.; Bentivoglio, M. Contralateral cortical projection to the mediodorsal thalamic nucleus: Origin and synaptic organization in the rat. Neuroscience 84:741–753; 1998.
50. Oda, S. Ultrastructure and distribution of corticothalamic fiber terminals from the posterior cingulate cortex and the presubiculum to the anteroventral thalamic nucleus of the rat. Brain Res. Bull. 42:485–491; 1997.
51. Ojima, H. Terminal morphology and distribution of corticothalamic fibers originating from layers 5 and 6 of cat primary auditory cortex. Cereb. Cortex 4:646–663; 1994.
52. Ojima, H.; Honda, C. N.; Jones, E. G. Characteristics of intracellularly injected infragranular pyramidal neurons in cat primary auditory cortex. Cereb. Cortex 2:197–216; 1992.
53. Ojima, H.; Murakami, K.; Kishi, K. Dual termination modes of corticothalamic fibers originating from pyramids of layers 5 and 6 in cat visual cortical area 17. Neurosci. Lett. 208:57–60; 1996.
54. Orman, S. S.; Humphrey, G. L. Effects of changes in cortical arousal and of auditory cortex cooling on neuronal activity in the medial geniculate body. Exp. Brain Res. 42:475–482; 1981.
55. Pandya, D. N.; Rosene, D. L.; Doolittle, A. M. Corticothalamic connections of auditory-related areas of the temporal lobe in the rhesus monkey. J. Comp. Neurol. 345:447–471; 1994.
56. Pontes, C. C.; Reis, F. F.; Sousa-Pinto, A. The auditory cortical projections onto the medial geniculate body in the cat: An anatomical study with silver and autoradiographic methods. Brain Res. 91:43–63; 1975.
57. Price, T. R.; Webster, K. E. The cortico-thalamic projection from the primary somatosensory cortex of the rat. Brain Res. 44:636–640; 1972.
58. Rinvik, E. Organization of thalamic connections from motor and somatosensory cortical areas in the cat. In: Frigyesi, T. L.; Rinvik, E.; Yahr, M. D., eds. Corticothalamic projections and sensorimotor activities. New York: Raven Press; 1972:57–90.
59. Robson, J. A.; Hall, W. C. The organization of the pulvinar in the grey squirrel (*Sciurus carolinensis*). I. Cytoarchitecture and connections. J. Comp. Neurol. 173:355–388; 1977.
60. Robson, J. A.; Hall, W. C. The organization of the pulvinar in the grey squirrel (*Sciurus carolinensis*). II. Synaptic organization and comparisons with the dorsal lateral geniculate nucleus. J. Comp. Neurol. 173:389–416; 1977.
61. Rockland, K. S. Further evidence for two types of corticopulvinar neurons. Neuroreport 5:1865–1868; 1994.
62. Rockland, K. S. Two types of corticopulvinar terminations: Round (type 2) and elongate (type 1). J. Comp. Neurol. 368:57–87; 1996.
63. Rodrigues-Dagaeff, C.; Simm, G.; de Ribaupierre, Y.; Villa, A.; de Ribaupierre, F.; Rouiller, E. M. Functional organization of the ventral division of the medial geniculate body of cat: Evidences for a rostrocaudal gradient of response properties and cortical projections. Hear. Res. 39:103–126; 1989.
64. Rouiller, E. M.; de Ribaupierre, F. Origin of afferents to physiologically defined regions of the medial geniculate body of the cat: Ventral and dorsal divisions. Hear. Res. 19:97–114; 1985.
65. Rouiller, E. M.; de Ribaupierre, F. Arborization of corticothalamic axons in the auditory thalamus of the cat: A PHA-L tracing study. Neurosci. Lett. 108:29–35; 1990.
66. Rouiller, E. M.; Welker, E. Morphology of corticothalamic terminals arising from the auditory cortex of the rat: A Phaseolus vulgaris-leucoagglutinin (PHA-L) tracing study. Hear. Res. 56:179–190; 1991.
67. Rouiller, E. M.; Liang, F.; Moret, V.; Wiesendanger, M. Patterns of corticothalamic terminations following injection of *Phaseolus vulgaris* leucoagglutinin (PHA-L) in the sensorimotor cortex of the rat. Neurosci. Lett. 125:93–97; 1991.
68. Rouiller, E. M.; Tanné, J.; Moret, V.; Kermadi, I.; Boussaoud, D.; Welker, E. Dual morphology and topography of the corticothalamic terminals originating from the primary, supplementary motor, and dorsal premotor cortical areas in macaque monkeys. J. Comp. Neurol. 396:169–185; 1998.
69. Rouiller, E. M.; Tanne, J.; Moret, V.; Boussaoud, D. Origin of thalamic inputs to the primary, premotor, and supplementary motor cortical areas and to area 46 in macaque monkeys: A multiple retrograde tracing study. J. Comp. Neurol. 409:131–152; 1999.
70. Ryugo, D. K.; Weinberger, N. M. Corticofugal modulation of the medial geniculate body. Exp. Neurol. 51:377–391; 1976.
71. Saldaña, E.; Feliciano, M.; Mugnaini, E. Distribution of descending projections from primary auditory neocortex to inferior colliculus mimics the topography of intracollicular projections. J. Comp. Neurol. 371:15–40; 1996.
72. Scannell, J. W.; Burns, G. A. P. C.; Hilgetag, C. C.; O'Neil, M. A.; Young, M. P. The connectional organization of the cortico-thalamic system of the cat. Cereb. Cortex 9:277–299; 1999.
73. Schwartz, M. L.; Dekker, J. J.; Goldman-Rakic, P. S. Dual mode of corticothalamic synaptic termination in the mediodorsal nucleus of the rhesus monkey. J. Comp. Neurol. 309:289–304; 1991.
74. Senft, S. L.; Woolsey, T. A. Growth of thalamic afferents into mouse barrel cortex. Cereb. Cortex 1:308–335; 1991.
75. Shinoda, Y.; et al. Thalamic terminal morphology and distribution of single corticothalamic axons originating from layers 5 and 6 of the cat motor cortex. Submitted for publication; 2001.
76. Sillito, A. M.; Cudeiro, J.; Murphy, P. C. Orientation sensitive elements in the corticofugal influence on centre-surround interactions in the dorsal lateral geniculate nucleus. Exp. Brain Res. 93:6–16; 1993.
77. Sillito, A. M.; Jones, H. E.; Gerstein, G. L.; West, D. C. Feature-linked synchronization of thalamic relay cell firing induced by feedback from the visual cortex. Nature 369:479–482; 1994.
78. Siwek, D. F.; Pandya, D. N. Prefrontal projections to the mediodorsal nucleus of the thalamus in the rhesus monkey. J. Comp. Neurol. 312:509–524; 1991.
79. Steriade, M. Synchronized activities of coupled oscillators in the cerebral cortex and thalamus at different levels of vigilance. Cereb. Cortex 7:583–604; 1997.
80. Steriade, M.; Timofeev, I.; Dürmüller, N.; Grenier, F. Dynamic properties of corticothalamic neurons and local cortical interneurons generating fast rhythmic (30–40 Hz) spike bursts. J. Neurophysiol. 79: 483–490; 1998.
81. Syka, J.; Popelar, J. Inferior colliculus in the rat: Neuronal responses to stimulation of the auditory cortex. Neurosci. Lett. 51:235–240; 1984.
82. Van der Loos, H. Barreloids in mouse somatosensory thalamus. Neurosci. Lett. 2:1–6; 1976.
83. Vidnyánszky, Z.; Görcs, T. J.; Négyessy, L.; Borostyánkoi, Z.; Kuhn, R.; Knöpfel, T.; Hámori, J. Immunocytochemical visualization of the mGluR1a metabotropic glutamate receptor at synapses of corticothalamic terminals originating from area 17 of the rat. Eur. J. Neurosci. 8:1061–1071; 1996.
84. Villa, A.; Abeles, M. Evidence for spatiotemporal firing patterns within the auditory thalamus of the cat. Brain Res. 509:325–327; 1990.
85. Villa, A. E. P.; Rouiller, E. M.; Simm, G. M.; Zurita, P.; de Ribaupierre, Y.; de Ribaupierre, F. Corticofugal modulation of the information processing in the auditory thalamus of the cat. Exp. Brain Res. 86: 506–517; 1991.
86. Villa, A. E. P.; Tetko, I. V.; Dutoit, P.; de Ribaupierre, Y.; de Ribaupierre, F. Corticofugal modulation of functional connectivity

within the auditory thalamus of rat, guinea pig and cat revealed by cooling deactivation. J. Neurosci. Methods 86:161–178; 1999.
87. Weedman, D. L.; Ryugo, D. K. Projections from auditory cortex to the cochlear nucleus in rats: Synapses on granule cell dendrites. J. Comp. Neurol. 371:311–324; 1996.
88. Weedman, D. L.; Ryugo, D. K. Pyramidal cells in primary auditory cortex project to cochlear nucleus in rat. Brain Res. 706:97–102; 1996.
89. Welker, E.; Hoogland, P. V.; van der Loos, H. Organization of feedback and feedforward projections of the barrel cortex: A PHA-L study in the mouse. Exp. Brain Res. 73:411–435; 1988.
90. Welker, E.; Armstrong-James, M.; Bronchti, G.; Ourednik, W.; Gheorghita-Baechler, F.; Dubois, R.; Guernsey, D. L.; van der Loos, H.; Neumann, P. E. Altered sensory processing in the somatosensory cortex of the mouse mutant barrelless. Science 271: 1864–1867; 1996.
91. Winer, J. A.; Larue, D. T. 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. 257:282–315; 1987.
92. Winer, J. A.; Larue, D. T.; Huang, C. L. Two systems of giant axon terminals in the cat medial geniculate body: Convergence of cortical and GABAergic inputs. J. Comp. Neurol. 413:181–197; 1999.
93. Wise, S. P.; Jones, E. G. Cells of origin and terminal distribution of descending projections of the rat somatic sensory cortex. J. Comp. Neurol. 175:129–158; 1977.
94. Wong, D.; Kelly, J. P. Differentially projecting cells in the individual layers of the auditory cortex: A double-labeling study. Brain Res. 230:362–366; 1981.
95. Woolsey, T. A.; Van der Loos, H. The structural organization of layer IV in the somatosensory region (SI) of mouse cerebral cortex. The description of a cortical field composed of discrete cytoarchitectonic units. Brain Res. 17:205–242; 1970.
96. Yeterian, E. H.; Pandya, D. N. Laminar origin of striatal and thalamic projections of the prefrontal cortex in rhesus monkeys. Exp. Brain Res. 99:383–398; 1994.