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The Thalamocortical Projection Systems in Primate: An Anatomical Support for Multisensory and Sensorimotor Interplay

Céline Cappe[1,2,4], Anne Morel[3], Pascal Barone[2] and Eric M. Rouiller[1]

[1]Unit of Physiology and Program in Neurosciences, Department of Medicine, Faculty of Sciences, University of Fribourg, Chemin du Musée 5, CH-1700 Fribourg, Switzerland, [2]Centre de Recherche Cerveau et Cognition, Unité Mixte de Recherche–Centre National de la Recherche Scientifique 5549, Université Paul Sabatier Toulouse 3 Faculté de Médecine de Rangueil, 31062 Toulouse Cedex 9, France, [3]Department of Functional Neurosurgery, Neurosurgery Clinic, University Hospital Zürich, Sternwartstrasse 6, CH-8091 Zürich, Switzerland and [4]The Functional Electrical Neuroimaging Laboratory, Neuropsychology and Neurorehabilitation Service and Radiology Service, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Rue du Bugnon 46, 1011 Lausanne, Switzerland

Multisensory and sensorimotor integrations are usually considered to occur in superior colliculus and cerebral cortex, but few studies proposed the thalamus as being involved in these integrative processes. We investigated whether the organization of the thalamocortical (TC) systems for different modalities partly overlap, representing an anatomical support for multisensory and sensorimotor interplay in thalamus. In 2 macaque monkeys, 6 neuroanatomical tracers were injected in the rostral and caudal auditory cortex, posterior parietal cortex (PE/PEa in area 5), and dorsal and ventral premotor cortical areas (PMd, PMv), demonstrating the existence of overlapping territories of thalamic projections to areas of different modalities (sensory and motor). TC projections, distinct from the ones arising from specific unimodal sensory nuclei, were observed from motor thalamus to PE/PEa or auditory cortex and from sensory thalamus to PMd/PMv. The central lateral nucleus and the mediodorsal nucleus project to all injected areas, but the most significant overlap across modalities was found in the medial pulvinar nucleus. The present results demonstrate the presence of thalamic territories integrating different sensory modalities with motor attributes. Based on the divergent/convergent pattern of TC and corticothalamic projections, 4 distinct mechanisms of multisensory and sensorimotor interplay are proposed.

Keywords: auditory system, corticothalamic, monkey, motor system, somatosensory system, tracing

Introduction

Recent electrophysiological studies reported short response latencies reflecting fast multisensory interplay (as proposed by Driver and Noesselt [2008], multisensory "interplay" is used instead of "integration" in order to include cases in which one modality is affected by another without strictly implying a unified percept) at low cortical level, for instance in the form of rapid somatosensory inputs to auditory cortex, both in monkeys (Schroeder et al. 2001; Schroeder and Foxe 2002; Fu et al. 2003; Brosch et al 2005; Lakatos et al. 2007) and in human subjects (Foxe et al. 2000; Murray et al. 2005). These rapid somatosensory–auditory interplays take place in low level auditory cortical areas traditionally regarded as unisensory, such as the belt auditory cortex (mainly caudiomedial auditory belt area or its human homologue), in line with functional Magnetic Resonance Imaging studies (Foxe et al. 2002; Kayser et al. 2005), although the primary auditory cortical area may also be involved (Lakatos et al. 2007). Audiovisual interplay was also observed at the same low level of the auditory cortex but less rapid due to slower visual signal transduction time (Giard and Peronnet 1999; Molholm et al. 2002; Schroeder and Foxe 2002; Kayser et al. 2007; Martuzzi et al. 2007; Meyer et al. 2007). Such rapid multisensory interplay at early cortical level is not compatible with the classical views of plurisynaptic corticocortical transmission via a sequential arrangement of multiple high hierarchical association cortical areas. Direct corticocortical routes between low level cortical areas of different modalities have been reported (Falchier et al. 2002; Rockland and Ojima 2003; Cappe and Barone 2005; Budinger et al. 2006), possibly contributing to the rapid multisensory interplay, although these direct connections are relatively sparse and characterized by slow propagation. An alternative mechanism, but not mutually exclusive, is the involvement of the thalamus in early multisensory interplay (see e.g., Driver and Noesselt 2008). For instance, multisensory information is already established at thalamic level (e.g., the medial division of the medial geniculate nucleus [MGN], medial pulvinar [PuM] nucleus), sending then feedforward thalamocortical (TC) projections to low level cortical areas (Morel et al. 1993; Hackett et al. 1998, 2007; Budinger et al. 2006; de la Mothe et al. 2006). An additional role for the thalamus in multisensory interplay may derive from the organization of its corticothalamic (CT) and TC loops. Indeed, the so-called feedforward CT projection originating from layer V in different sensory or motor cortical areas represents a fast and secure pathway by which, combined with a subsequent TC projection, information can be transferred between remote cortical areas through a "cortico-thalamo-cortical" route (see e.g., Guillery 1995; Rouiller and Welker 2000; Sherman and Guillery 2002, 2005; Sherman 2007). In this context, it is crucial to establish in detail the divergence/convergence of thalamic projections to cortical areas representing different modalities. As previous anatomical studies on TC interconnections were focused on specific projections, the present study aimed at extending these data to the issue of multisensory interplay. As low level auditory cortical areas in the macaque monkey were demonstrated to be the site of rapid somatosensory–auditory interplay (see above), we injected retrograde tracers in the auditory cortex, coupled to injections of other tracers in somatosensory area 5 to elucidate which thalamic nuclei and which circuits connected with the cerebral cortex are involved in such multisensory interplay. Furthermore, as integration of 2 or more senses is well known to enhance behavioral performance (e.g., increased probability of detection/identification and decrease of reaction time), as

compared with unimodal stimulation, it was also important to decipher the sensorimotor circuits by which behavioral facilitation may occur. For this reason, representing an originality of the present study, our investigation of multisensory interplay was extended to the motor side as well, by injecting in the same monkey retrograde tracers also in the premotor cortex, in addition to the injections aimed at the auditory and somatosensory cortices.

Materials and Methods

Injections of 6 neuroanatomical tracers were performed in each of 2 monkeys (MK1 and MK2) in various areas of the posterior parietal cortex, the auditory cortex, and the premotor cortex (see inset Fig. 1) to retrogradely label the corresponding TC neurons. Data derived from one of these tracers, biotinylated dextran amine (BDA), yielding not only retrograde labeling in the thalamus as the other tracers but even more prominently anterograde labeling, were reported in a recent study (Cappe, Morel, and Rouiller 2007): BDA was injected in both monkeys in the posterior parietal associative cortex (area 5), thus allowing to study in detail the pattern of its CT projection. In the present study, we focused more specifically on the TC projections and investigated how they can provide a basis for multisensory and sensorimotor interplay. The experiments described in this report were conducted on 2 adult monkeys, 1 *Macaca mulatta* (MK1) and 1 *Macaca fascicularis* (MK2), 3 and 4 years old and weighing 3 and 4 kgs, respectively. All experimental procedures followed the Guide

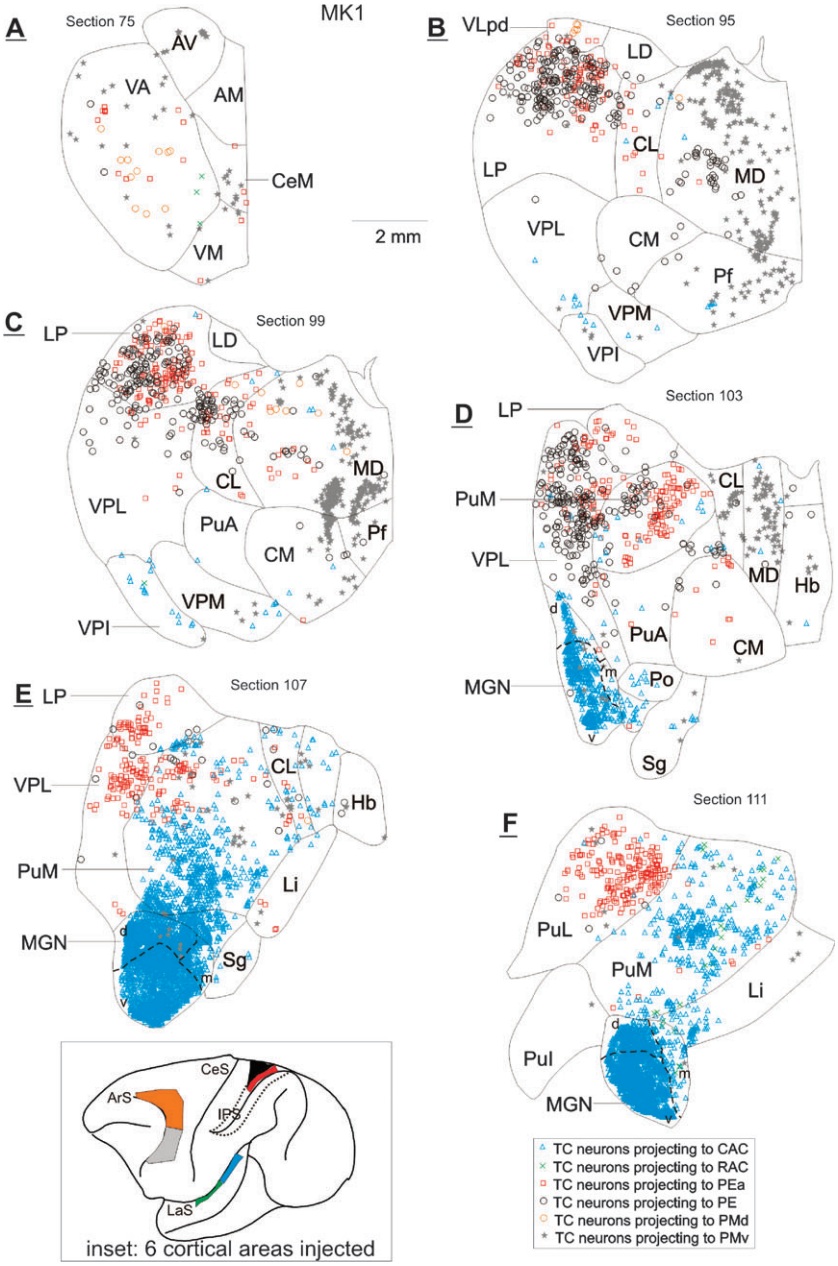


Figure 1. Distribution of retrograde (TC neurons) labeling in MK1 in the thalamus after injections of DY in area PMd (open orange circles), WGA in area PMv (gray stars), FB in CAC (open blue triangles), FE in RAC (green crosses), BDA in area PE (open black circles), and FR in area PEa (open red squares). Frontal sections are arranged from rostral to caudal (75–111). For a more complete representation of the retrograde labeling on a larger number of sections, see Supplementary Figure 3. The color of the symbols and the symbols correspond to the same injected areas in the 2 monkeys. The inset of the Figure shows the 6 cortical areas injected with the tracers in the 2 monkeys included in the present study. See list of abbreviations.

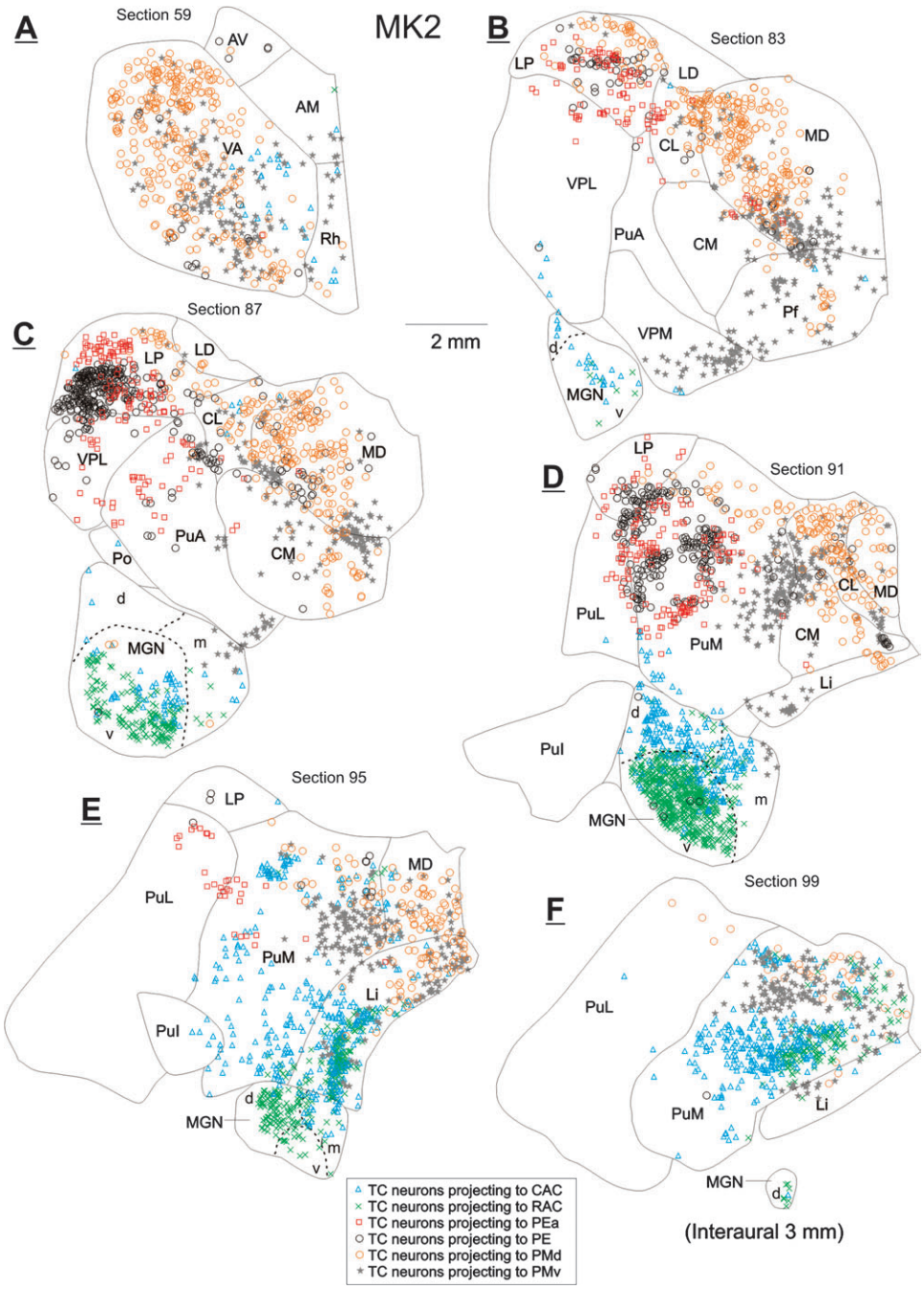


Figure 2. Distribution of retrograde (TC neurons) labeling in MK2 in the thalamus after injections of FE in area PMd (open orange circles), FB in area PMv (gray stars), FR in CAC (open blue triangles), DY in RAC (green crosses), WGA in area PE (open black circles), and BDA in area PEa (open red squares). Frontal sections are arranged from rostral to caudal (59–99). For a more complete representation of the retrograde labeling on a larger number of sections, see Supplementary Figure 4. See list of abbreviations.

for the Care and Use of Laboratory Animals (ISBN 0-309-05377-3; 1996) and were approved by local (Swiss) veterinary authorities.

Tracer Injections

The 6 neuroanatomical tracers were pressure injected in 6 cortical areas at multiple sites (inset Fig. 1; Supplementary Figs 1 and 2): 1) The rostral portion of the auditory cortex (RAC), including mainly the so-called rostral belt/parabelt of the auditory cortex; 2) The caudal portion of the auditory cortex (CAC), including mainly the so-called caudal belt/parabelt of the auditory cortex; 3) Area PE of the posterior parietal cortex (in area 5); 4) Area PEa of the posterior parietal cortex (in area 5); 5) The dorsal premotor cortical area (PMd) and; 6) The ventral premotor cortical area (PMv). Examples of injection sites and thalamic retrograde labeling are illustrated in Supplementary Figure 1. More detailed representations of the multiple deposits of each tracer in the different cortical areas are shown in Supplementary Figure 2 for the auditory and premotor cortex and in a recent report for area 5 (Cappe, Morel, and Rouiller 2007).

The following neuroanatomical tracers were used: fast blue (FB; Fluka, Switzerland), fluoroemerald (FE; Molecular Probes, Eugene, OR), diamidino yellow (DY; Sigma Aldrich, France), fluororuby (FR; Molecular Probes), BDA (Molecular Probes), wheat germ agglutinin (WGA; Sigma Aldrich), and cholera toxin B subunit (CB; List Biological

Laboratories, Campbell, CA). Detailed information on the locations of injections, the tracers injected and the amounts delivered are given in Supplementary Table 1. The results concerning the anterograde and retrograde labeling after injection in area 5 (PE and PEa) were described separately in another report (Cappe, Morel, and Rouiller 2007), but we used here the retrograde data to compare the thalamic connections of area 5 with the other cortical areas (RAC, CAC, PMd, and PMv) injected in the present study. The tracer injections and the histological processing were performed following experimental procedures previously described in detail (Rouiller et al. 1998, 1999, 2003; Liu et al. 2002; Tanné-Gariépy, Boussaoud, and Rouiller 2002; Tanné-Gariépy, Rouiller, and Boussaoud 2002; Cappe, Morel, and Rouiller 2007) and available in the Supplementary Materials and Methods. The cortical areas in PM and area 5 were determined based on criteria previously defined (Boussaoud et al. 2005; Cappe, Morel, and Rouiller 2007), based essentially on the marker SMI-32.

Data Analysis

The retrogradely labeled cells, forming thalamic territories projecting to the different cortical areas injected, were each represented by a symbol specific for each tracer on serial drawings of sections of the thalamus (Figs 1 and 2), where nuclear borders were delineated on the basis of Nissl and acetylcholinesterase stainings (see Supplementary Materials and Methods). The relative contribution of inputs from different thalamic nuclei to RAC, CAC, PEa, PE, PMd, and PMv areas was assessed by counting, for each tracer injected, the number of labeled cells in each thalamic nucleus and by calculating the percentage of the total number of cells labeled with this particular tracer (Fig. 3).

In addition, in order to assess the extent of overlap between the thalamic territories projecting to distinct cortical areas, an "index of overlap" was calculated, as previously reported (Tanné-Gariépy, Boussaoud, and Rouiller 2002; Morel et al. 2005) and explained in detail in the Supplementary Materials and Methods. The index of overlap (Fig. 4) may range between 2 extreme values: 0% when 2 thalamic territories projecting to 2 distinct cortical areas are spatially completely segregated and 100% when the 2 thalamic territories fully overlap (considering a spatial resolution of 0.5 mm). This analysis provides a kind of "voxel-like" (0.5 mm by 0.5 mm) estimates of thalamic territories where spatial overlap of 2 tracers takes place, irrespective of the absolute number of TC cells labeled with each individual tracer.

Results

Localization of Injection Sites

As outlined in the Introduction section, multisensory interplay may already be present in primary cortical areas but to a limited extent. For this reason, the auditory, somatosensory, and motor cortical areas targeted with the tracers are located at low hierarchical levels, while showing strong evidences of multisensory or sensorimotor interplay. More specifically, in both MK1 and MK2, 6 injections of different tracers were aimed at the caudal and rostral parts of the auditory cortex (CAC and RAC, respectively), areas PE and PEa (in area 5), and the dorsal and ventral premotor cortex (PMd and PMv, respectively). The tracer covered a significant portion of each cortical area and spread on all cortical layers (Supplementary Figs 1 and 2). Along the rostrocaudal axis, typically the injected zones extended over 4 mm for the small injections up to 8 mm for the large injections. However, the multiple injections with a given tracer did not form a continuous territory but rather a patchy mosaic. Although the injections covered a substantial zone of the targeted cortical area, the tracer was far from filling the entire corresponding cortical area.

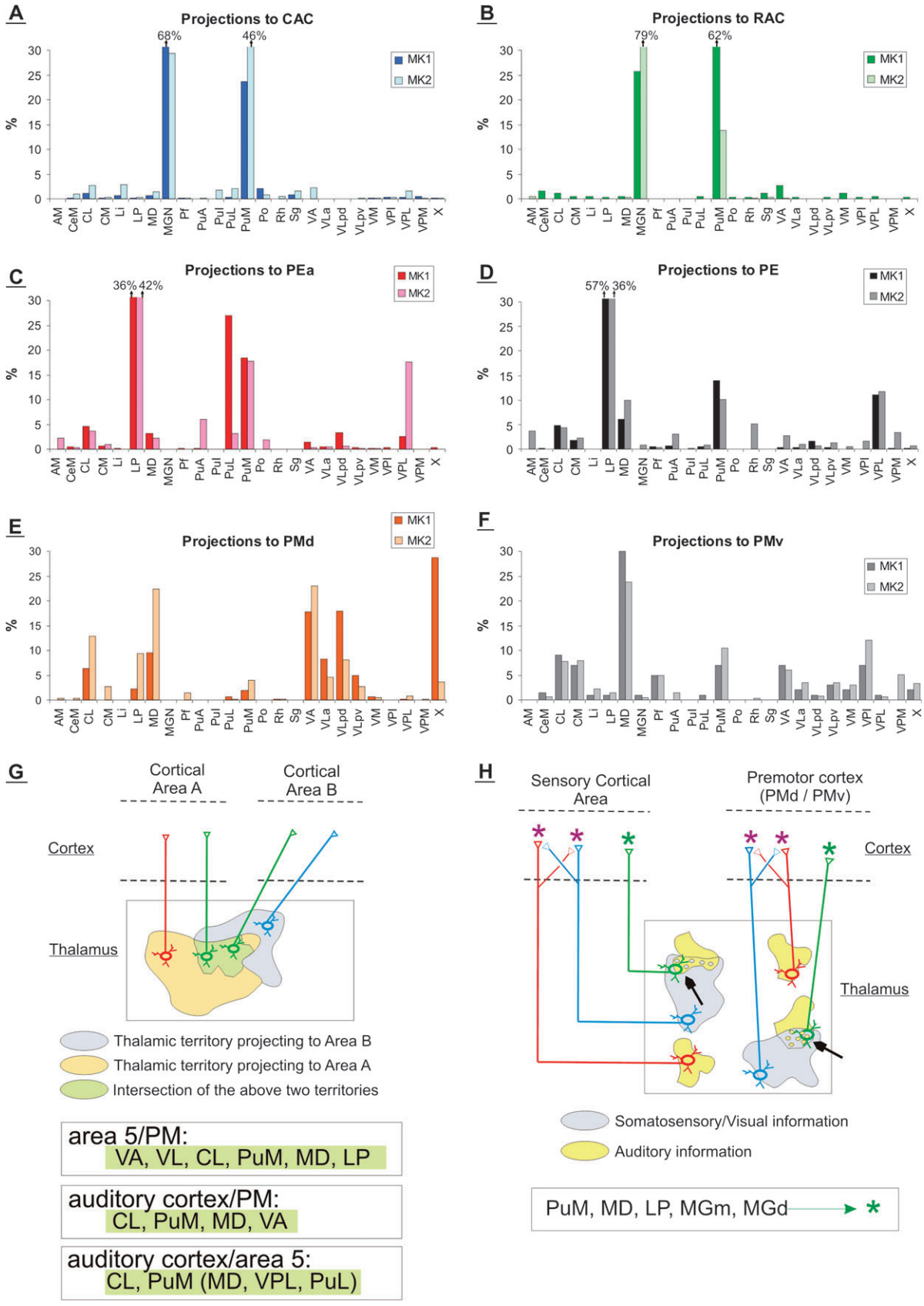
In the auditory cortex, except for MK1 where a single injection aimed at RAC was restricted to the rostral auditory parabelt (Supplementary Fig. 1G), other injections in RAC (MK2) and CAC (MK1 and MK2) covered parts of the rostral and caudal auditory parabelt areas and, more medially in the ventral bank of the lateral sulcus, the belt areas (especially the caudolateral and caudomedial auditory belt areas caudally) as well as, but to a lesser extent, the auditory core (Supplementary Fig. 2, panels A and B). In the case of the injection in CAC in MK2, in one penetration the syringe penetrated too deeply and the tracer encroached probably to the superior temporal polysensory area but was restricted to the infragranular layers (Supplementary Fig. 2, panel A, section 110).

TC Projections to Each of the 6 Injected Cortical Areas

The overall distribution of retrogradely labeled neurons in thalamus following injections of tracers in the different cortical areas is shown in Figures 1 and 2, for MK1 and MK2, respectively (more comprehensive reconstructions of retrogradely labeled neurons are available in Supplementary Figs 3 and 4). For both monkeys, the retrogradely labeled neurons were distributed along the entire rostrocaudal extent of the thalamus but were clearly more numerous anteriorly after injections in premotor cortex (PMd and PMv) and posteriorly after injections in auditory (CAC and RAC) and somatosensory (areas PE and PEa) cortices. The major source of thalamic inputs to each cortical domain was from modality dominant thalamic nuclei, that is, motor nuclei (ventral anterior nucleus [VA], VL, and area X) to the premotor cortex, in particular PMd, somatosensory nuclei (lateral posterior nucleus [LP] and ventral posterior lateral nucleus [VPL]) to areas PE and PEa, and auditory nuclei (MGN subdivisions) to CAC and RAC (see also Fig. 3).

In the auditory cortex, the TC neurons projecting to CAC (case MK2) were located mainly in the dorsal (d) and medial (m) divisions of the MGN, although few labeled cells were also found rostrally in the ventral (v) division of the MGN (Figs 1 and 2; Supplementary Fig. 5). As a result of a larger CAC injection, with spread into the auditory core (case MK1), more abundant

Figure 3. Quantitative distribution of the TC projections directed to the auditory, premotor, and parietal cortical areas. (*A–F*) Histograms of the percentages of labeled cells in each thalamic nucleus with respect to the total number of cells in the thalamus labeled after injection in each cortical area. For each histogram and each monkey, the sum of all bins is 100% and only projections representing more than 0.5% of total are included (see text). See list of abbreviations. (*G*) In some thalamic nuclei, territories project to a cortical area A (yellow area) and others to a cortical area B (blue area). Such territories may partly overlap, corresponding to a restricted thalamic region (green area) where a given information computed by TC neurons (green symbols) will be sent in a divergent mode to the remote cortical areas A and B. The bottom 3 rectangles indicate the thalamic nuclei where such overlap of origins is present for the projections directed to area 5/PM, auditory cortex/PM, and auditory cortex/area 5, respectively. (*H*) Thalamic nuclei considered as multisensory, containing neurons carrying somatosensory or visual (blue area) and/or auditory (yellow area) information, send TC projections to different sensory or premotor cortical areas. In subregions of such multisensory thalamic nuclei, somatosensory or visual and auditory information may even be present in the same TC neurons or in adjacent ones (zones of overlap of blue and yellow territories, pointed by black arrows). As a result, a multisensory information is relayed by TC neurons (green symbols) to sensory cortical areas or to the premotor cortex, allowing rapid sensorimotor interplay. The bottom rectangle indicates the thalamic nuclei containing multisensory information, transferred then to the cerebral cortex via TC projection (pathway aimed to the green asterisk). The figure also illustrates the mechanism of convergence of 2 TC projections (aimed to the purple asterisks), one originating from one modality (auditory) and the other from a different modality (somatosensory or visual). Although such convergence is represented in the form of axon collaterals near the target in the cortex, it is most likely that 2 distinct adjacent TC neurons project to the zone depicted by the purple asterisks.


A
Projections to CAC
68%
46%
MK1
MK2
%
AM CeM CL CM Li LP MD MGN Pf PuA PuI PuL PuM Po Rh Sg VA VLa VLpd VLpv VM VPI VPL VPM X
B
Projections to RAC
79%
62%
C
Projections to PEa
36%
42%
D
Projections to PE
57%
36%
E
Projections to PMd
F
Projections to PMv
G
Cortical Area A
Cortical Area B
Cortex
Thalamus
Thalamic territory projecting to Area B
Thalamic territory projecting to Area A
Intersection of the above two territories
area 5/PM:
VA, VL, CL, PuM, MD, LP
auditory cortex/PM:
CL, PuM, MD, VA
auditory cortex/area 5:
CL, PuM (MD, VPL, PuL)
H
Sensory Cortical Area
Premotor cortex (PMd / PMv)
Cortex
Thalamus
Somatosensory/Visual information
Auditory information
PuM, MD, LP, MGm, MGd

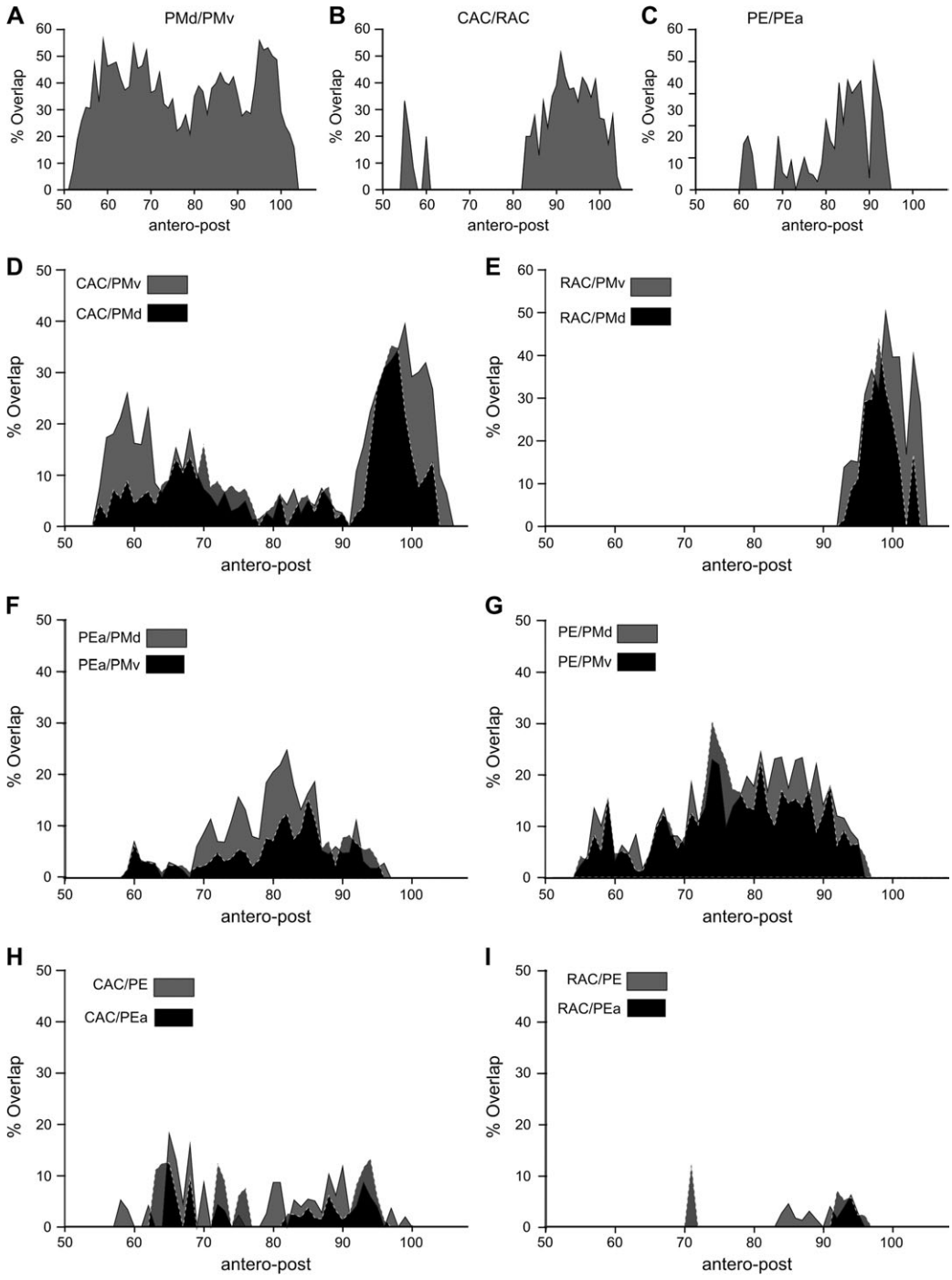


Figure 4. Overlap versus segregation of thalamic territories projecting to areas PMd/PMv (*A*), to areas CAC/RAC (*B*), to areas PE/PEa (*C*), to areas CAC/PMd (black area) and CAC/PMv (gray area) (*D*), to areas RAC/PMd and RAC/PMv (*E*), to areas PEa/PMd and PEa/PMv (*F*), to areas PE/PMd and PE/PMv (*G*), to areas CAC/PEa and CAC/PE (*H*), and to areas RAC/PEa and RAC/PE (*I*), plotted as a function of the anteroposterior location of the corresponding section of the thalamus in MK2. The positions of sections are numbered 50–110, from rostral to caudal, as illustrated in Supplementary Figure 4, and intervals between sections are 200 μm. See list of abbreviations.

retrograde labeling was found in the MGN, particularly in the ventral division (Fig. 1). Most TC cells projecting to RAC were in ventral division of the MGN in case MK2 where the injection also included the core, but consistent labeling was also found in medial division of the MGN [MGm] and in the posterior part of dorsal division of the MGN [MGd] (Fig. 2; Supplementary Fig. 5). As a result of a single injection in RAC limited to parabelt (case MK1), a moderate retrograde labeling was found in the MGN (mainly in MGd and MGm). These results focusing on the thalamic projections to the auditory cortex are discussed further in the "Supplementary Discussion."

In addition to the above modality dominant thalamic inputs, other thalamic nuclei are the origin of quantitatively weak to moderate, TC projections, considered here as nonmodality specific. For instance, in MK2 (Figs 2 and 5), the injections in PMd and PMv yielded fairly abundant retrograde labeling in

nuclei located in middle and caudal portions of the thalamus, in particular not only in LP and mediodorsal nucleus (MD) but also in PuM, centre median nucleus (CM)-parafascicular nucleus [Pf], central lateral nucleus (CL), and limitans nucleus (Li). Consistent data with MK2 were obtained in MK1 (Fig. 1), especially for PMv, although relatively weak retrograde labeling was found as a result of DY injection in PMd. A sparse projection from the MGN to the premotor cortex (PMd/PMv) was also observed in each case (Figs 1 and 2; Supplementary Figs 3 and 4).

As far as area 5 is concerned (PE and PEa), besides its main TC projection from LP and VPL, inputs were also found to originate from the thalamic nuclei PuM, VA, VL, CL, MD, anterior pulvinar (PuA), and lateral pulvinar (PuL) (Figs 1, 2, and 5; Supplementary Figs 3 and 4), representing TC connections providing potentially multisensory and/or sensorimotor interplay. In addition, we have observed a sparse projection from the MGN to area PE (sections 87–91 in Fig. 2).

For the auditory cortex (in the large sense), besides the main TC input from the MGN, other thalamic nuclei send projection to RAC and CAC, such as PuM, representing a quantitatively substantial source of inputs (Table 1, Figs 1, 2, and 5; Supplementary Figs 3–5). The projection from PuM to the CAC involved the lateral and rostral portion of the nucleus but, progressing more caudally, the medial part also contained labeled cells. In contrast, the projection from PuM to the RAC appears more restricted, limited to the caudomedial part of PuM (Supplementary Fig. 5). We also found significant retrograde labeling in the Li after injections in RAC and CAC, including the Sg-Lim zone referred to by Hackett et al. (1998). As a result of tracer injection in CAC (and to a lesser extent in RAC), modest retrograde labeling was also found in the CL, VA, VL, MD, and PuL nuclei (Figs 1 and 2; Supplementary Fig. 5). There was also a very sparse projection from VPL to CAC in both monkeys.

Quantitative Analysis of the TC Strength of Projection

The relative contribution of the different thalamic nuclei to the TC projections directed toward the 6 cortical areas injected was quantified for each monkey (Table 1 and Fig. 3). For simplification, only the thalamic nuclei from which projections exceeded 0.5% to at least one injected area were taken into consideration. As described above and illustrated in Figures 1 and 2, the thalamic nuclei known to be specific for a given cortical area indeed exhibited strong projections to this area. For instance, in MK1, the CAC receives 68% of its thalamic projections from the MGN, in particular from the ventral division. A clearly predominant labeling was present in the MGN in that case because the injections covered not only the caudal belt/parabelt but also the auditory core. In contrast, in MK2, the percentage of labeled neurons in the MGN after injection in the CAC amounted only to about 30% because the injections were mainly in the parabelt, thus producing more labeling in PuM than in MGN (Fig. 3*A*). The proportions of labeled neurons in MGN and PuM after injections in the RAC were reversed in the 2 monkeys (Fig. 3*B*): In MK1 with an injection mainly in the rostral parabelt, labeled neurons were more numerous in PuM than in MGN (62% and 26%, respectively), whereas in MK2, the injections spread in the lateral belt and, to a lesser extent, also in the core, thus producing more retrograde labeling in the MGN, in particular the ventral division, than in PuM (79% and 14%, respectively) (Fig. 3*B*). The areas PE and PEa receive clearly more inputs

Table 1
Relative strength (in %) of TC projections possibly involved for multisensory and sensorimotor interplay

		RAC	CAC	PE	PEa	PMd	PMv
PuM	MK1	62.3	23.7	13.9	18.4	2	7
	MK2	13.8	45.8	10.1	17.7	4	10.5
MD	MK1	0.8	0.8	6.1	3.1	9.5	30
	MK2	0.4	1.4	10	2.3	22.3	23.8
LP	MK1	0.4	0.3	57.4	35.9	2.2	1
	MK2	0	0.3	35.6	42.1	9.4	1.5
VA	MK1	2.8	0.1	0.4	1.5	17.8	7
	MK2	0.3	2.2	2.7	0.4	23	6.1
CL	MK1	1.1	1.2	4.8	4.6	6.3	9
	MK2	0	2.8	4.3	3.7	12.8	7.7
CM	MK1	0.6	0.3	1.8	0.8	0	7
	MK2	0	0.3	2.3	1	2.7	7.9
VPL	MK1	0.6	0.3	11.1	2.6	0.3	1
	MK2	0	1.6	11.8	17.6	0.8	0.6

from the LP nucleus than from any other thalamic nuclei in both monkeys, but the contributions of the pulvinar, in particular PuM, and of VPL are also substantial (Figs 3*C*,*D*). As far as PMd and PMv are concerned, the main sources of thalamic inputs are shared by the motor nuclei VA, VL, and area X as well as by MD (Figs 3*E*,*F*). However, the proportions of neurons in these nuclei differ according to the premotor area injected: higher proportions in MD, but lower proportions in motor nuclei, after PMv injection as compared with PMd injections. Nevertheless, the quantification in Figure 3*A*–*F* confirmed the notion that each cortical area receives consistent convergent inputs from a fairly large number of thalamic nuclei, ranging from less than 1% to 10–25% of the total number of TC labeled neurons. Conversely, most thalamic nuclei project to more than one cortical area injected in this study. Those with divergent projections to all 6 areas are listed in Table 1. In both monkeys, the PuM nucleus projects to all areas injected but overall more strongly to CAC and RAC than to PE, PEa, PMv, and PMd. Similarly, MD projects to all areas injected, though more strongly to PMd, PMv, PE, and PEa than to CAC and RAC. We found also stronger projections from LP and VPL to PE, PEa, PMd, and PMv than to CAC and RAC. VA sends strong projections to the premotor cortex (especially PMd) but much less to the auditory and parietal cortices. The CL and CM nuclei project to all 6 cortical areas in various proportions, reaching up to 13% for the CL projection to PMd in MK2. The small nucleus central medial nucleus (CeM) projects to RAC (only in MK1) and CAC, PEa, PE, PMd (only for MK2), and PMv, representing a small proportion of all TC projections not exceeding 2% (to RAC in MK1). Finally, PuL and Li also project to the different injected cortical areas (except on area PE in MK1 for Li and on RAC and PMv in MK2 for PuL), again representing small proportions of the overall TC projections.

The divergence and convergence of TC projections to different cortical areas belonging to distinct modalities are schematically represented in Figure 3*G*–*H*. The divergent mode allows a given uni- or multisensory information to be sent simultaneously to remote sensory and/or motor cortical areas (Fig. 3*G*). In the convergent mode, as shown by the histograms in Figure 3*A*–*F*, a given cortical area receives inputs from different thalamic nuclei or territories relaying somewhat distinct modalities (e.g., projections from PuM and LP converging onto PMd). As a result, a given cortical territory will receive spatially convergent TC inputs creating a multimodal territory in the cortex (Fig. 3*H*, purple stars

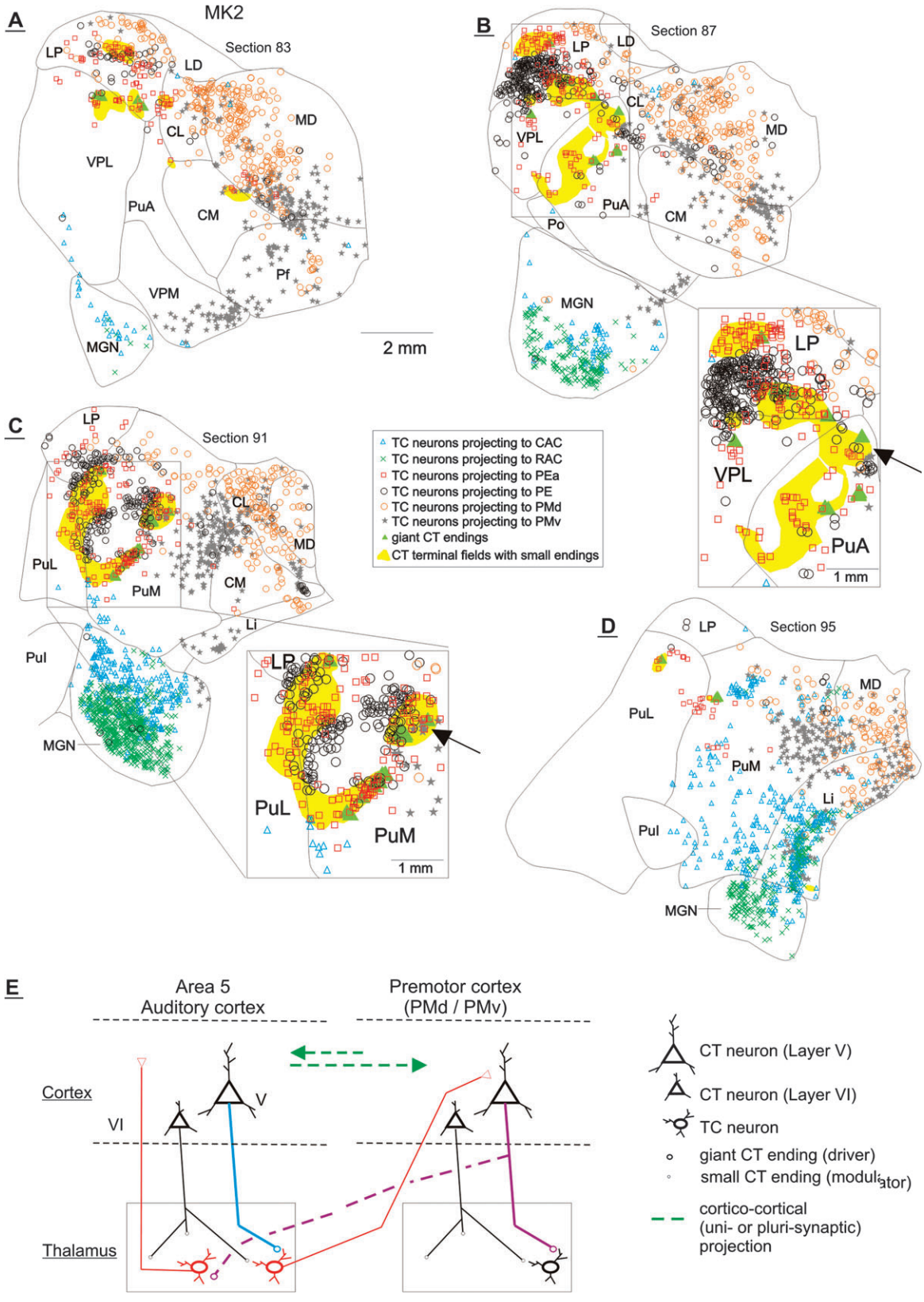


Figure 5. In (*A–D*), distribution of retrograde (TC neurons) and anterograde (corticothalamic [CT] terminal fields) labeling in MK2 in the thalamus after injections of FE in area PMd (open orange circles), FB in area PMv (gray stars), FR in CAC (open blue triangles), DY in RAC (green crosses), WGA in area PE (open black circles), and BDA in area PEa (open red squares for TC neurons, yellow territories for small CT endings, and green filled triangles for giant CT endings). Frontal sections are arranged from rostral to caudal (83–95). (*E*) CT neurons in layer VI of either area 5 or auditory cortex send "modulatory" (feedback) projections to the thalamus terminating with small endings, whereas CT neurons in layer V are the origin of "drive" (feedforward) projections (blue line) to the thalamus terminating with giant endings. By contacting TC (TC) neurons in the thalamus, the giant endings are in position to transfer transthalamically sensory information to the premotor cortex (red TC axon terminating in PMd and PMv). The cortico-thalamic-cortical routes illustrated here represent an alternative to corticocortical pathways (green dashed arrows), believed to be slower and less secure.

representing a somatosensory–auditory interplay or a visuoauditory interplay).

Overlap of TC Projections to Different Sensory and Motor Cortical Areas

Although the thalamic projections to cortical areas of distinct modality are largely segregated (see above), as proposed in Figure 3*G*, there are subterritories, particularly in nonspecific thalamic nuclei, where TC projections to cortical areas of distinct modality exhibit overlap to various degrees (Figs 1 and 2). For instance, in VA, the origin of minor projections directed to PE (black open circles) and to CAC (blue triangles) coincides with territories sending strong projections to PMd and PMv (Fig. 2*A*). Similarly, the origin of the projection from MD to PE is overlapping with territories containing neurons projecting to PMd and PMv (Figs 1*B* and 2*B–D*). In the LP nucleus, source of dense TC projections to PE and PEa, the territories of origin also contain neurons projecting to the premotor cortex, though more to PMd than to PMv. CL is also a thalamic nucleus where TC cross-modal overlap takes place: projections to PMd and PMv exhibit some overlap with neurons projecting to PE and/or PEa (Fig. 2*B–D*) as well as with neurons projecting to auditory cortex (Figs 1*E* and 2*C*). Finally, in PuM, an overlap between projections to PE and/or PEa and to the premotor cortex was observed (Figs 1*D,E* and 2*D,E*) as well as between the territories projecting to the auditory cortex (more to CAC than to RAC) and to the premotor cortex (Figs 1*D,E* and 2*E,F*). Coincidence of territories projecting to the 2 sensory cortical areas (area 5 and auditory cortex) was also present in PuM (Figs 1*D–F* and 2*D–F*). The main thalamic nuclei exhibiting overlap of the origins of their projections to area 5, auditory cortex, and premotor cortex, taken 2 by 2, are summarized in the bottom 3 rectangles of Figure 3*G*.

Quantitative Assessment of Overlap of TC Projections

As previously reported (Tanné-Gariépy, Boussaoud, and Rouiller 2002; Morel et al. 2005; Cappe, Morel, and Rouiller 2007), we quantified the degree of superimposition between the origins of projections by taking 2 by 2 the different combinations of retrograde tracers, using an index of overlap. The results are presented in Figure 4 for the data derived from MK2.

Overlap between Projections to Areas of a Same Modality

As expected, we found a quite extensive overlap between the origins of projection to PMd and PMv (35% overlap on average along the entire thalamus; Fig. 4*A*), in line with the overlap between the projections to the areas PMd-c and PMv-c with the same methods of calculation (Morel et al. 2005). This overlap takes place in ventral lateral posterior nucleus, ventral division (VLpv), ventral lateral posterior nucleus, dorsal division (VLpd), ventral medial nucleus, VA, area X, MD, PuM, CL, and Li. The overlap between the origins of projection to CAC and RAC is substantial (on average up to 22% for MK1 and 32% for MK2; see Fig. 4*B*) but only in the caudal part of the thalamus (MGN, PuM). The average overlap between the origins of projection to PE and PEa is 20% for both monkeys on the whole thalamus, whereas, for the caudal part of the thalamus only, the average overlap amounts up to 36% for MK1 and 26% for MK2 (Fig. 4*C*). The thalamic inputs to areas PE and PEa are overlapping mainly at the level of LP, PuM, PuA, and VPL.

Overlap between Projections to Areas of Different Modalities

Thalamic territories sending TC projections to cortical areas of different modalities are relatively limited. However, they may exhibit a substantial degree of spatial overlap and thus contribute to multisensory and sensorimotor interplay. In some cases, such overlap may be restricted to a limited portion of the rostrocaudal extent of the thalamus. Considering the entire thalamus, the projection to the auditory and the premotor cortices originates in both monkeys from thalamic territories overlapping between 4% and 12%, whereas for the caudal part of the thalamus only, the average overlap raises up to 40–50% (in MK2) (Fig. 4*D,E*). Projections to premotor and auditory cortex overlap in several nuclei, mainly in PuM, CL, and SG-Li but also in VA (medial part), MD, CeM, CM-Pf, and MGN. The most prominent overlap takes place in CL, MD, and PuM for both monkeys. It corresponds mainly to projections to CAC and PMv or PMd. The thalamic territories projecting to the premotor and the parietal cortex overlap to a substantial extent, reaching 20% (Fig. 4*F,G*). It concerned mainly VA, ventral lateral anterior nucleus (VLa), VLpd, CL, MD, and PuM for both cases. We also found such overlap in PuL for MK1 (Fig. 1 and Supplementary Fig. 3) and in VLpv, LP, and CM for MK2 (Fig. 2 and Supplementary Fig. 4). The main thalamic nuclei with overlapping projections to the auditory and the parietal cortex are CL, PuM, and, to a lesser extent, VPL for both monkeys. In MK2, projections to these 2 areas also overlap in MD and PuL. There is more overlap between projections directed to CAC and PE as well as to CAC and PEa than between the projections to RAC and to 1 of the 2 subregions of area 5 (Fig. 4*H,I*). In fact, the thalamic projections to RAC overlap with those directed to PEa or PE only up to 5% and only for a very limited portion of the rostrocaudal extent of the thalamus (Fig. 4*I*).

In summary, this quantification of overlapping thalamic territories shows, for the projections to cortical areas of different modality, a territory of overlap mostly at the level of the posterior thalamus (Fig. 4*D–I*). PuM appears to be the thalamic nucleus where overlapping origins of projections to the different injected cortical areas are predominant. In consequence, we focused our analysis on this nucleus and performed a precise quantification of the amount of overlap in PuM. This analysis revealed a strong but comparable degree of superimposition of the origins of projections directed to CAC and PMd, CAC and PMv, RAC and PMd, and RAC and PMv, ranging from 14% to 20%. Overlap of TC projections to area 5 (PE or PEa) and the auditory areas (CAC or RAC) or to area 5 and premotor cortex (PMd or PMv) amounts to 5% at most.

TC Projections to the Different Cortical Areas in Relation to CT Projections from Parietal Areas

As described in a previous study (Cappe, Morel, and Rouiller 2007), CT projections originating from the parietal areas PE and PEa were analyzed in the same monkeys. Area PE sends CT projections with small endings to LP, VPL, and PuM and, but less densely, to VLpd, CL, and CM. Area PE also sends CT projections with giant endings to LP, VPL, and PuM (Fig. 3 in Cappe, Morel, and Rouiller 2007). As shown in Figure 5, area PEa projects mainly with small endings to LP, VPL, PuL, PuM, and PuA as well as to ventral posterior inferior nucleus, CL, MD, and CM. The CT projections from area PEa formed by giant endings terminate mainly in LP, VPL, PuA, and PuM and also in MD and PuL. Thus, as illustrated in Figure 5, PuM, PuA, LP, and

VPL that receive input via giant endings from area PEa project in turn to auditory, parietal, and premotor areas. This is the case also for CM, CL, and MD but to a lesser extent (data not shown). At higher magnification (Fig. 5*B*,*C*: arrows), some giant CT endings originating from PEa (green triangles) are close to TC neurons projecting to PMv (gray stars). The few giant CT endings shown in Figure 5 resulted from small injection sites in PEa (Fig. 2 in Cappe, Morel, and Rouiller 2007). One should consider that in case of much larger injections of dyes, filling the entire PEa and then the giant CT endings would have been far more numerous, thus creating many more and closer appositions with TC neurons projecting in turn to the premotor cortex or to the auditory cortex.

Discussion

Possible Mechanisms of Multimodal Interplay in the Thalamus

The present data on thalamic connections with the auditory cortex, area 5, and premotor cortex support the notion of early multimodal interplay involving the thalamus, based at least on 4 possible mechanisms.

First, we present evidence that a restricted thalamic territory sends divergent projections to remote cortical areas (Fig. 3*G*), thus providing simultaneous inputs which can then be mixed with different intrinsic sensory and/or motor attributes. For example, the overlap of thalamic territories interconnected with area 5 and auditory belt/parabelt may represent an anatomical support for TC transfer of somatosensory information to auditory areas or, reciprocally, auditory information to associative parietal areas (Supplementary Fig. 8 and Discussion). Although such a kind of multimodal integration in the temporal domain cannot be excluded (in case, the inputs reach the cerebral cortex at the exact same time), it is less likely to provide massive multimodal interplay than an actual spatial convergence of projections. More plausible is the possibility that such a temporal coincidence mechanism may serve as a synchronizer of activities in remote cortical locations resulting in a higher perceptual saliency of multimodal stimuli (Fries et al 2001).

Second, more pertinent for multimodal interplay is a TC projection relaying rapidly to the cerebral cortex, an integrated multimodal information already established in the thalamus, for instance in PuM, LP, MD, MGm, or MGd, where several modalities have already converged (Fig. 3*H*). As our injections included the cortical layer I, it is likely that some of these projections providing multimodal information to the cortex originate from the so-called "matrix" calbindin-immunoreactive neurons distributed in all thalamic nuclei and projecting diffusely and relatively widely to the cortex (Jones 1998). In PuM, considerable mixing of territories projecting to cortical areas belonging to several modalities is in line with previously reported connections with several cortical domains, including visual (e.g., Baleydier and Morel 1992; Rockland 1996; Weller et al. 2002), auditory (Morel et al. 1993; Hackett et al. 1998), somatosensory (Burton and Jones 1976; Baleydier and Maugiere 1977), and prefrontal and motor (Romanski et al. 1997; Morel et al. 2005) areas. Neurons in PuM respond to visual (Gattass et al. 1979) and auditory stimuli (Yirmiya and Hocherman 1987), in line with a contribution to processing of movements directed in space (Acuna et al. 1983). Similarly, MD also exhibits a consistent overlapping pattern and is principally interconnected with multisensory areas of prefrontal and premotor cortices (Goldman-Rakic and Porrino 1985; Giguere and Goldman-Rakic 1988; Matelli et al. 1989; Matelli and Luppino 1996; Rouiller et al. 1999; Morel et al. 2005), thus representing a key structure for working memory (Funahashi et al. 2004). In monkeys, MD neurons also respond to visual, auditory, and odorant stimuli (Yarita et al. 1980; Tanibuchi and Goldman-Rakic 2003).

Third, as outlined in Figure 3*H*, a given cortical territory receives TC inputs originating from distinct thalamic territories engaged in the processing of different modalities (visual, somatosensory, auditory, and motor). The spatially converging inputs at cortical level (ideally on an individual neuron or on adjacent neurons) may result in fast multimodal interplay. For instance, the convergence of TC projections from PuM and LP onto area 5 (Fig. 3*C*,*D*) may represent the anatomical support for rapid somatosensory–auditory interplay in area 5. Even more relevant in a behavioral context are for instance convergent TC projections from PuM and LP onto the premotor cortex (Fig. 3*E*,*F*), a circuit allowing rapid use of combined somatosensory–auditory information in order to produce a fast movement in response to the association of the 2 stimuli. The counterpart of such rapid multisensory integration used to produce synergistically fast motor responses may account for the decrease in reaction times generally observed in response to bimodal stimuli in man (Welch and Warren 1986) and monkey (Cappe, Loquet, et al. 2007). Because the restricted number of injected areas already leads to a wide distribution of the origins of TC inputs (Fig. 3*A*–*F*), it suggests that such a mechanism of convergence plays an important role for multimodal interactions. More work needs to be done on how precise is such spatial convergence (does the multimodal information converge on individual neurons?).

Fourth, as shown in Figure 5, LP and area 5 (PE/PEa) are strongly interconnected (Cappe, Morel, and Rouiller 2007) and the corresponding CT terminal fields overlap not only with its reciprocal TC projection but also with thalamic territories in LP projecting to premotor cortex. Consequently, information originating from area 5 may be transferred transthalamically to PMd and PMv (Fig. 5*E*, Supplementary Fig. 6 and Discussion). As some of the CT projection from PE and PEa involves the giant terminals associated to feedforward type of transmission, the transthalamic transfer of information from area 5 to premotor cortex is synaptically secure and fast (Guillery 1995; Rouiller and Welker 2000; Sherman and Guillery 2005; Sherman 2007), most likely faster than plurisynaptic corticocortical projections from area 5 to premotor cortex (green dashed arrow in Fig. 5*E*). The cortico-thalamo-cortical route for rapid transfer of information from area 5 to premotor cortex is actually reciprocal (Supplementary Fig. 6) and can support a rapid transfer of motor attributes from premotor cortex to the associative somatosensory area, an information pertinent for active sensory exploration (palpation) for instance. Transthalamic loops connecting remote cortical areas and involving feedforward CT projections terminating with giant endings were demonstrated in many thalamic areas (e.g., Schwartz et al. 1991; Rockland 1996; Darian-Smith et al. 1999; Rouiller et al. 1998, 2003; Taktakishvili et al. 2002; Rouiller and Durif 2004) and compatible with fast transthalamic interactions at large scale between distant cortical regions (Feig and Harting 1998; Sherman and Guillery 2002; Van Horn and Sherman 2004;

Sherman 2007). The same concept of cortico-thalamo-cortical route may apply to PuM. The partial overlap observed in PuM between projections to auditory and premotor cortex allows thalamic transfer of auditory information to the frontal lobe providing support for audio-motor integration (Supplementary Fig. 6 and Discussion).

In the above 4 proposed mechanisms of multimodal interplay, the number of neurons involved or contributing to territories of overlap or to convergence of projections in some areas appears fairly modest and therefore of functionally limited influence. The issue of setting a minimal percentage for the density of a projection to be functionally relevant is however far from being trivial. For instance, the projection of the lateral geniculate nucleus onto the primary visual cortex (V1) represents only 5% of the entire cortical inputs to V1 (and only a few % of all synapses present in layer IV in V1, see Latawiec et al. 2000). Nevertheless, without such projection, the pattern of activity in many visual cortical areas is dramatically modified. In the monkey, only a sparse direct projection had been reported from AI to V1 (Falchier et al 2002), although such pathway represents probably the anatomical support of the decrease in visual latency of V1 neurons in visuoauditory conditions (Wang et al 2008). In other words, a projection though quantitatively limited may still exert a functionally substantial influence. This may also be the case of the thalamic territories of overlap and/or of convergent projections reported in the present study. For example, TC projections from specific nuclei such as the somatosensory VPL may contribute to multisensory interplay, via its projections toward the auditory and premotor cortices (Fig. 3), an observation also true for the MGN projections to area 5 and premotor cortex but to a lesser extent.

Multimodal Interplay in the Thalamus Relevant for Rapid Executive Functions

Several cortical areas contribute to multisensory integration (for review, see Ghazanfar and Schroeder 2006; Driver and Noesselt 2008). For instance, the premotor cortex is a polymodal integration area, with convergence of visual, auditory, and somatosensory inputs (e.g., Graziano and Gandhi 2000; Graziano 2001), an information related to motor intention used for preparation of voluntary movement (e.g., Boussaoud et al. 1995). Multimodal inputs to the premotor cortex originate, among many sources of inputs, from multisensory parietal areas (Johnson et al. 1996; Shipp et al. 1998; Luppino et al. 1999; Tanné-Gariépy, Rouiller, and Boussaoud 2002). Response latencies to sensory stimuli in premotor cortex may be short, in line with the present study demonstrating a fairly direct access via the thalamus. PuM is the main candidate thalamic nucleus (present study; see also Crick and Koch 1998; Shipp 2003), by which information from different sensory modalities can converge to premotor cortex based on its connectivity with numerous cortical areas (e.g., Romanski et al. 1997; Hackett et al. 1998; Gutierrez et al. 2000). Lastly, in line with the above concept of TC loop allowing fast multimodal interplay, motor influences may be rapidly conveyed to sensory areas. Such mechanism may account for behavioral encoding observed at neuronal level in visual and auditory areas in the form of responses influenced by behavioral meaning of the stimulus (Wurtz and Mohler 1976; Benson et al. 1981; Vaadia et al. 1982; Colby et al. 1996; Mazzoni et al. 1996; Durif et al. 2003).

Conclusions

Multisensory integration was shown to occur in the cat superior colliculus (for a review, Stein and Meredith 1993; Meredith 2002), delineating key principles for investigating multisensory integration in other species and brain structures. The present study puts forward that, in agreement with recent data (Hackett et al. 2007), in addition to the corticocortical pathways, TC loops participate to the integration of different modalities (Supplementary Discussion) and to the expression of multisensory and sensorimotor integration at behavioral level.

Supplementary Material

Supplementary Figures 1–8, Table 1, Materials and Methods, Abbreviation List, and Discussion can be found at: http://www.cercor.oxfordjournals.org/.

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Address correspondence to email: eric.rouiller@unifr.ch.

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