Heteromodal connections supporting multisensory integration at low levels of cortical processing in the monkey

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Abstract

While multisensory integration is thought to occur in higher hierarchical cortical areas, recent studies in man and monkey have revealed plurisensory modulations of activity in areas previously thought to be unimodal. To determine the cortical network involved in multisensory interactions, we performed multiple injections of different retrograde tracers in unimodal auditory (core), somatosensory (1/3b) and visual (V2 and MT) cortical areas of the marmoset. We found three types of heteromodal connections linking unimodal sensory areas. Visuo-somatosensory projections were observed originating from visual areas [probably the ventral and dorsal fundus of the superior temporal area (FSTv and FSTd), and middle temporal crescent (MTc)] toward areas 1/3b. Somatosensory projections to the auditory cortex were present from S2 and the anterior bank of the lateral sulcus. Finally, a visuo-auditory projection arises from an area anterior to the superior temporal sulcus (STS) toward the auditory core. Injections in different sensory regions allow us to define the frontal convexity and the temporal opercular caudal cortex as putative polysensory areas. A quantitative analysis of the laminar distribution of projecting neurons showed that heteromodal connections could be either feedback or feedforward. Taken together, our results provide the anatomical pathway for multisensory integration at low levels of information processing in the primate and argue against a strict hierarchical model.

Introduction

The widely accepted model of information processing states in the CNS that visual, tactile and auditory information are processed from the peripheral to the cortical level through separate channels that target primary sensory cortices from which information is further distributed to functionally specialized areas. Despite this apparent separation between modalities, we can simultaneously integrate different sensory signals, resulting in percepts distinct from those derived from a single unimodal experience (Stein & Meredith, 1993). Psychophysical studies have demonstrated that multisensory integration results in perceptual improvement by reducing ambiguity (Welch & Warren, 1986). For example, the detection of a visual target or orientation toward it is strongly facilitated when it is associated with an auditory stimulus (Frens & Van Opstal, 1995; Goldring et al., 1996; McDonald et al., 2000; Vroomen & de Gelder, 2000). However, using specific temporal and spatial features of stimulation, multisensory interactions can alter perception leading to illusory phenomena (Shams et al., 2000; Maeda et al., 2004), such as ventriloquism (Spence & Driver, 2000; Slutsky & Recanzone, 2001) or the 'McGurk effect' (McGurk & MacDonald, 1976). While visuo-auditory interactions have been most frequently studied (Lovelace et al., 2003; Zwiers et al., 2003), crossmodal interactions can involve many different combinations of modalities and of perceptual features. For example, tactile discrimination can be influenced by both vision and audition (Guest et al., 2002; Guest & Spence, 2003; Spence & Driver, 2004). Regarding visuo-auditory integration, apart from spatial attributes, other aspects of visual perception can be modulated by intersensory interactions such

as shape discrimination (Dufour, 1999) or intensity judgement (Stein et al., 1996). Overall, these results suggest the existence of specific cortical pathways, which link functionally specialized areas across each modality and are involved in processing particular features of multisensory integration.

Evidence for perceptual interactions between sensory modalities is now well established, but their neuronal substrate is poorly understood apart from the superior colliculus, which constitutes a model for studying multisensory integration at a single cell level (Meredith & Stein, 1983; Wallace et al., 1992; Stein, 1998). In the primate, the frontal, parietal and temporal lobes contain neurons responding to more than one modality (Baylis et al., 1987; Mistlin & Perrett, 1990; Calvert et al., 2000; Downar et al., 2000; Bremmer et al., 2001; Graziano, 2001), and consequently have been identified as sites of multimodal integration (Calvert et al., 1998). It is generally accepted that sensory modalities converge in these higher level areas through feedforward pathways. However, the notion that multisensory integration is restricted to high order areas has recently been challenged by anatomical (Falchier et al., 2002; Rockland & Ojima, 2003) imaging (Sathian et al., 1997; Calvert et al., 2000; Laurienti et al., 2002) and electrophysiological data (Giard & Peronnet, 1999; Foxe et al., 2000; Schroeder & Foxe, 2004). These studies have revealed that crossmodal interactions can occur in unimodal areas at very early levels of cortical processing. This original concept suggests the existence of a cortical network that directly links unimodal areas allowing rapid and adaptive behaviour in response to multimodal stimulation. In this study, using anatomical tracers in the marmoset, our results show that heteromodal connections are indeed present at hierarchical stages below the classically defined polysensory areas. Second, the pattern of laminar origin of these heteromodal connections suggests that the direction of

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flow of information between connected areas can be either feedforward or feedback.

Materials and methods

Surgery and injection of retrograde tracers.

The common marmoset (*Callithrix jacchus*) is a New World primate with a lissencephalic cortex, unlike Old World monkeys, such as the macaque, in which more than 50% of the cortical surface is buried into numerous sulci. This feature offers the great advantage of making visual, somatosensory and auditory cortical areas easily accessible to tracer injections. In all cases sterile surgical procedures were followed. Prior to surgery, the animal received a single dose of valium (3 mg/kg, i.m.) and atropine (0.2 mg/kg, i.m.). Thirty minutes later, the marmoset was anaesthetized with ketamine hydrochloride (25 mg/kg, i.m.) and xylazine (5 mg/kg, i.m.). Dexamethasone (0.3 mg/kg, i.m.) was also administered to prevent cerebral oedema. Additional doses of ketamine hydrochloride (half of initial dose) were administered as needed to maintain a surgical level of anaesthesia. During surgery, heart rate, respiration rate and body temperature were monitored, the latter being maintained at 38 °C through an electric blanket.

Once the animal was anaesthetized, the skin was cut, the temporal muscle retracted, and a craniotomy performed over the auditory, somatosensory and visual cortices. Anatomic landmarks, in particular the lateral sulcus (LaS) and the fundus of the temporal sulcus, were used to guide the injections of tracers in the different areas of interest. In this study, four adult marmosets had received simultaneous injections of retrograde tracers (Fig. 1) in known unimodal auditory ($n = 4$, belt and core), somato-motor ($n = 3$, areas 1/3b or area 4) and visual [$n = 2$, areas V2 and middle temporal (MT)] cortical areas. Injections in the auditory cortex were performed along the caudal part

in the lower bank of the LaS. Injections in the somatosensory cortex were made at a distance of 3–6 mm medial to the tip of the LaS. To reach area MT we made injections at 2.5 mm perpendicular to the tip of the LaS based on previous electrophysiological characterization of this area (Rosa & Tweedale, 2000). To locate area V2 we followed the characteristic higher vascular network on the surface of area V1 and placed our injection immediately anterior to the V1/V2 border. Hamilton syringes, in some cases equipped with a glass micropipette (60–80 μm diameter), were used to inject 0.2–0.3 μL of retrograde fluorescent tracers: fluororuby (FR-10% in H_2O), fluoroemerald (FE-10% in H_2O), diamidino yellow (DY-3% in NaCl) and subunit B of cholera toxin (CB-2% in H_2O). Most of the injections were made perpendicular to the cortical surface at a depth of about 800 μm and consisted of one or two injections of dyes. In one case (02–14) the injections were elongated and parallel to the cortex and spanned 2 mm in length. After completion of the injections, a sterile contact lens was positioned over the exposed cortex, the dural flaps placed over the lens, the bone of the skull was put back and then covered by dental acrylic cement. The cranial muscles and the skin were sutured. Each animal was monitored closely during the 10–13 days survival time corresponding to the optimal period for the transport of the tracers. In three cases, before being perfused, animals were used in an acute electrophysiological recording session made under anaesthesia in area V1 contralateral to the injected hemisphere. All the procedures used follow the National and EEC regulations concerning animal experiments and have been approved by the authorized ethical committee (Ref MP/01/01/01/05).

Histological processing

After the survival period, animals were given a lethal dose of pentobarbital before being perfused intracardially with 0.9% saline containing 0.1% heparin, followed by 4% paraformaldehyde in

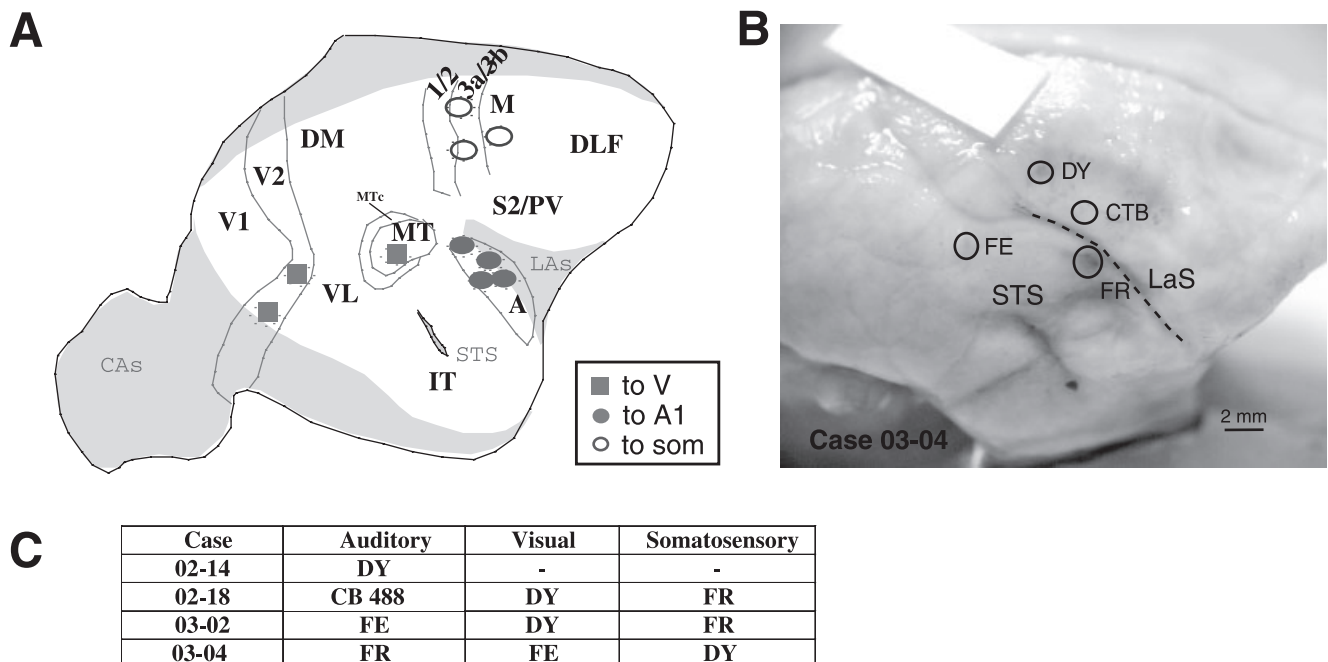| Case	Auditory	Visual	Somatosensory
02-14	DY	-	-
02-18	CB 488	DY	FR
03-02	FE	DY	FR
03-04	FR	FE	DY

FIG. 1. (A) Location of injection sites for all cases presented on a schematic view of a marmoset brain areas (Rosa *et al.*, 2005). Each blob indicates a single injection located in auditory (filled circles), visual (squares) or somatosensory (open circles) areas. (B) Photograph of a fixed brain on which are shown the simultaneous dye injections in different sensory areas (case 03-04). (C) Summary table of the experimental cases and the retrograde tracers injected into different sensory areas. CB, cholera toxin botulic; DY, Dyamidino-Yellow; FB, Fast-blue; FE, fluoroemerald; FR, fluororuby; LaS, lateral sulcus; STS, superior temporal sulcus.

phosphate buffer pH 7.4. Brains were immediately removed and put in sucrose solutions of increasing concentrations (10, 20 and 30%) for cryoprotection. Parasagittal serial sections (40 μm thick) were made on a freezing microtome. Alternate sections were reacted for neuronal alkaline phosphatase (NAP; Fonta *et al.*, 2004, 2005), cytochrome oxidase (CO; Wong-Riley, 1979), myelin (Gallyas, 1979) or stained for Nissl substance with Cresyl violet.

Data analysis

Sections were observed using light or fluorescent microscopy with a Leica microscope (DMR) equipped with a CCD camera. Images were acquired using a software (Mosaic, Explora Nova®) installed on a computer directly linked to the microscope stage. For each cortical area the exact position of labelled neurons was computed on individual sections spaced at regular intervals using Mercator software (Explora Nova®). Sampling frequencies of analysed sections were adjusted to the size of the areas containing labelled neurons (defined as the projection zone). This allowed us to construct a density profile of the projection, which represents the distribution across the brain of the number of retrogradely labelled neurons counted in individual sections (Fig. 2E). In all graphs of density profiles, values (given in mm) correspond to the separation from the first section cut in the parasagittal plane.

In every labelled area a density distribution of projection neurons was constructed for labelled cells in both infra- and supragranular layers. The laminar location of projection neurons was derived from adjacent sections stained for histological markers (Nissl, CO, NAP). The laminar distribution of the labelled neurons in individual projection zones is one criteria for defining the feedforward (FF) or feedback (FB) anatomical nature of the cortico-cortical connections (Rockland & Pandya, 1979). FF projections originate mainly from upper layers, while FB projections arise from lower layers. For each labelled area (or projection zone) we calculated the percentage infra [%infra = (number of neurons in infra)/(total number in infra + supra)] and percentage supra [%supra = (number of neurons in supra)/(total number in infra + supra)], and used this number to classify the projections. Based on previous studies on the anatomical definition of cortical connections (Barone *et al.*, 2000; Hilgetag & Grant, 2001), projections having a value of percentage infra greater than 55% were classified as FB and those with values of percentage supra greater than 55% were classified as FF. Values between these two limits were defined as lateral connections.

Results

Injection sites

Our study aimed to explore the existence of direct connections between sensory areas thought to be unimodal in order to define the network involved in multisensory integration. To do so it was important to define precisely the location of the individual dye injections and the associated areas containing labelled neurons. In the New World monkey, the basic cortical organization of sensory areas is similar to that described in the macaque monkey, although the homology of some areas between macaque and marmoset still need further clarification (Kaas, 1997; Rosa, 1997). In the present study we have adopted the nomenclature of areas proposed by Rosa and collaborators (Rosa & Elston, 1998; Rosa & Tweedale, 2000).

Auditory cortex injections

Four injections were made in the auditory cortex of four marmosets (Fig. 2). The injection sites were about 1.2 mm in diameter and all of
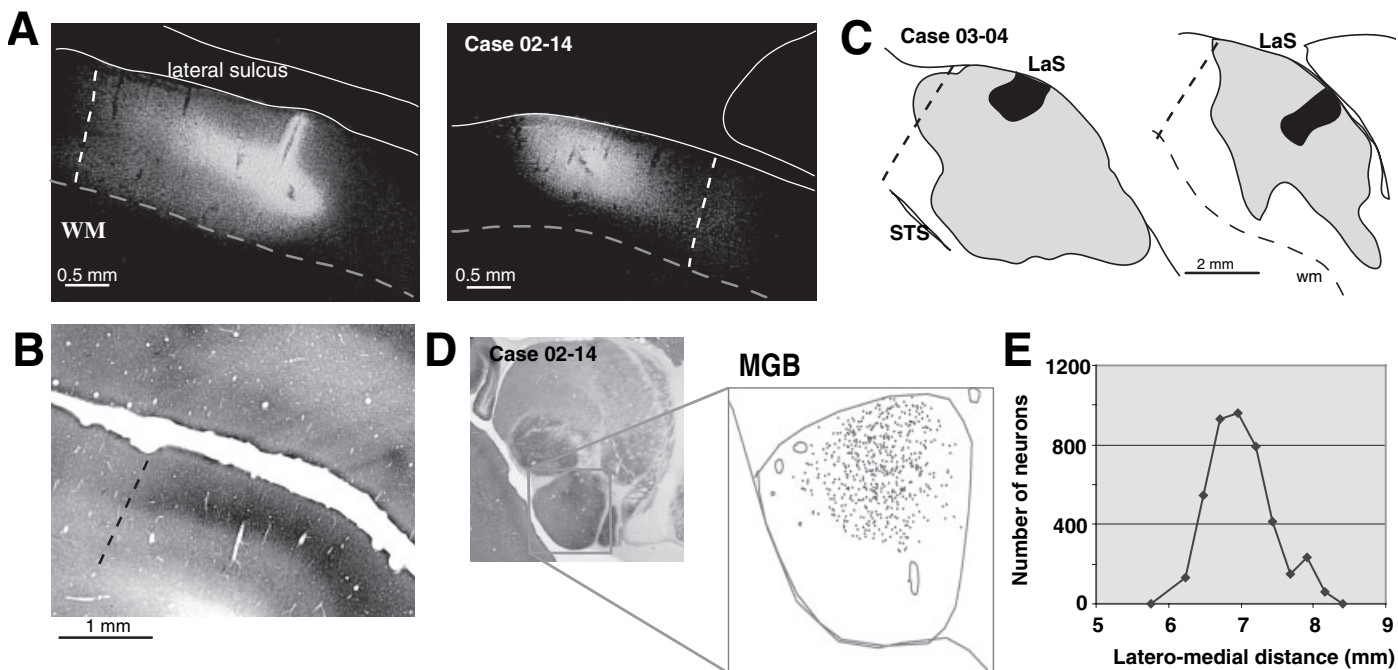

FIG. 2. Injection site in the auditory cortex (A). Photomicrograph of a parasagittal section showing a Dyamidino-Yellow (DY) injection site in the posterior bank of the LaS corresponding to the auditory cortex. Left panel shows that part of the injection is located in the core but spread posteriorly outside the core as shown in the right panel. Dashed line indicates the posterior limit of the core as seen from an adjacent section (B) stained for CO activity. (C) Another example of an injection site in the auditory core (case 03-04) on two parasagittal sections. The black region indicates the deposit of dye and the grey area represents the extent of the zone of uptake. In this case the injection is most exclusively restricted to the core. (D) Distribution of labelled neurons in the medial geniculate body (MGB), following the DY injection illustrated in (A). Each dot represents a retrogradely labelled neuron. The MGB limits were defined using CO staining on adjacent sections. (E) Density profile of the MGB projection to the auditory cortex. The 'zero' value on the *x*-axis corresponds to the first section cut in the sagittal plane.
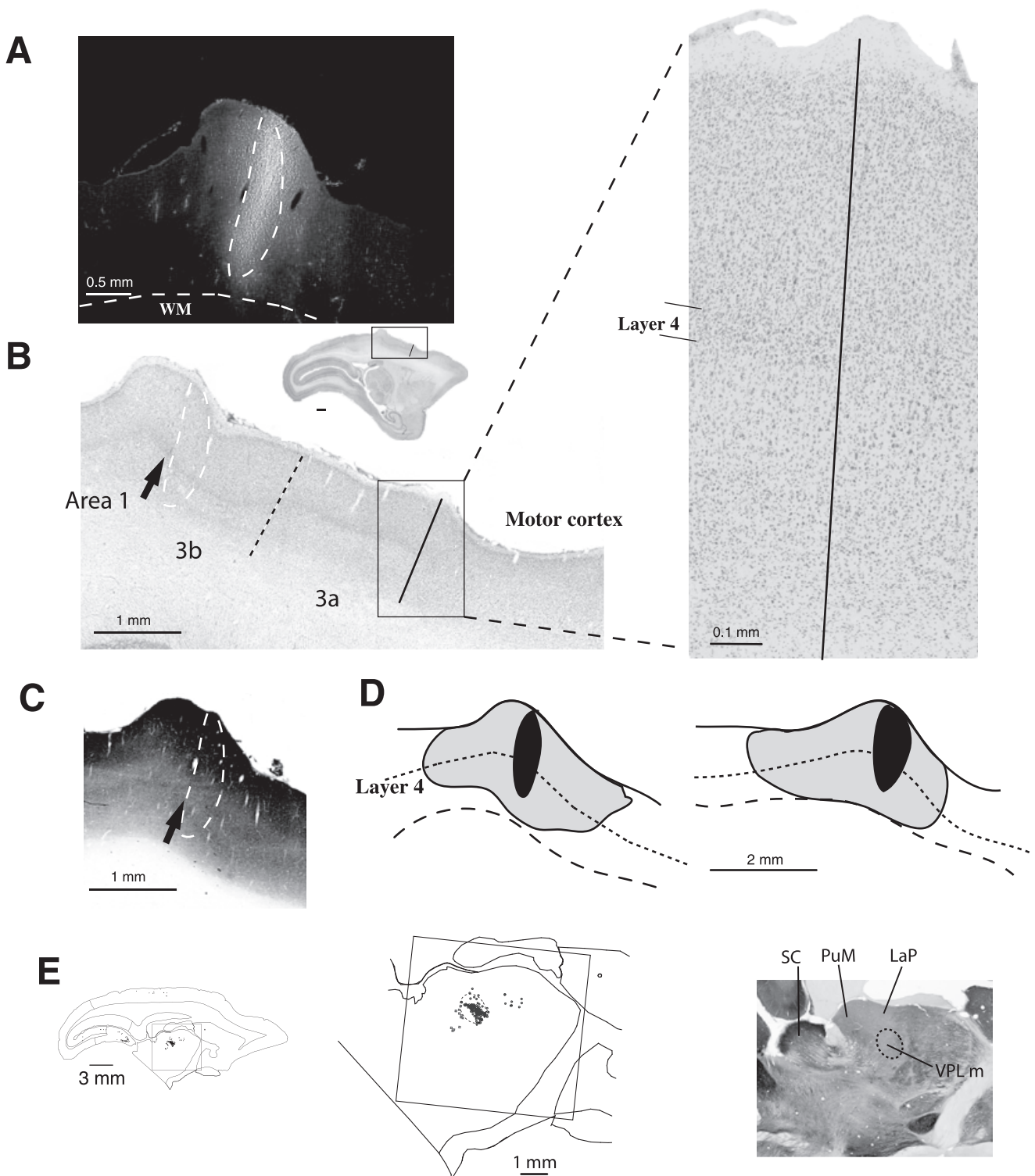
FIG. 3. Injection site in the somatosensory cortex (case 03-02). (A) Photomicrograph of a fluororuby (FR) injection site on a parasagittal section. The Nissl staining (B) shows the border between the somatosensory and the motor cortex (arrow), the latter being characterized by a poorly defined layer 4 and the presence of Betz cells in layer 5 as seen on the enlarged view on the right panel. The antero-posterior location of the injected area (square) is illustrated on the entire view of the corresponding parasagittal section. The distinction between 3a and 3b (dashed line) is suggested by a more pronounced layer 5 and a thinner layer 4 in 3a in addition to a more higher lamination in 3b. (C) Location of the border between area 1 and area 3b (black arrow) observed on a separate section reacted to cytochrome oxidase. Area 3b shows a higher CO expression in layer 4 compared with the adjacent area 1. This shows that our injection site is located in area 3b and invades area 1. (D) Drawing of the extent of the injection site observed on two parasagittal sections. (E) Thalamic labelling following an injection in areas 1/3b. Projection neurons are located in the medial part of the VPL nucleus as located in the right panel on a cytochrome oxidase-reacted section. PuM, medial pulvinar nucleus; SC, superior colliculus.
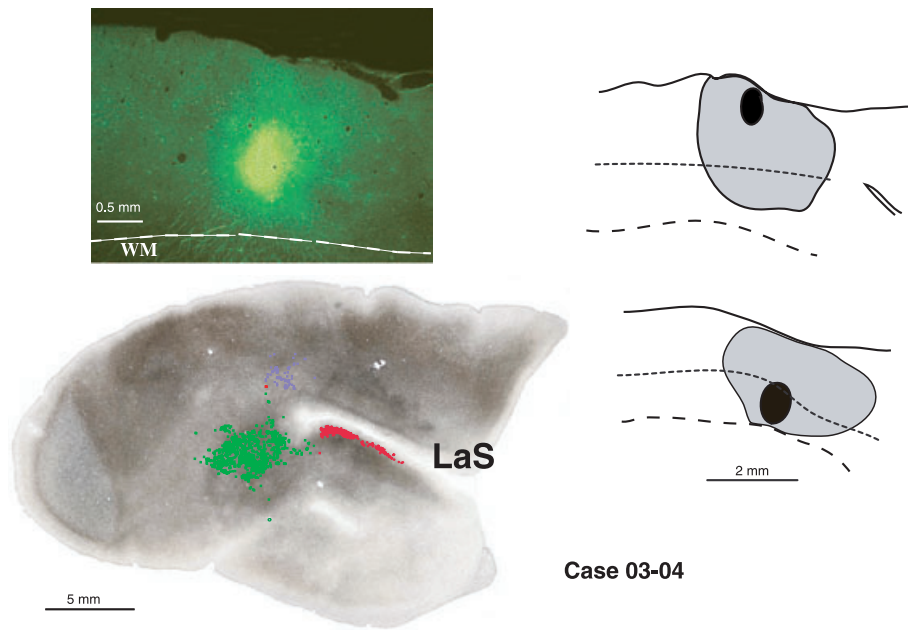
FIG. 4. Injection site in area MT. (A) Photomicrograph of a fluoroemerald (FE) injection site in area MT on a parasagittal section. (B) The location of the injection site in area MT is confirmed by the presence of callosally projecting cells (green dots) restricted to the highly myelinated zone corresponding to the contralateral area MT. Blue and red dots represent callosal projecting neurons labelled after injections of dyes, respectively, in the somatosensory cortex and the auditory core. Note that the somatosensory callosal neurons are located in a restricted region, corresponding probably to areas 1 and 3b∕3a. (C) Drawing of the extent of the injection site in MT observed on two parasagittal sections.

Visual projections from the inferotemporal cortex to the somatosensory areas
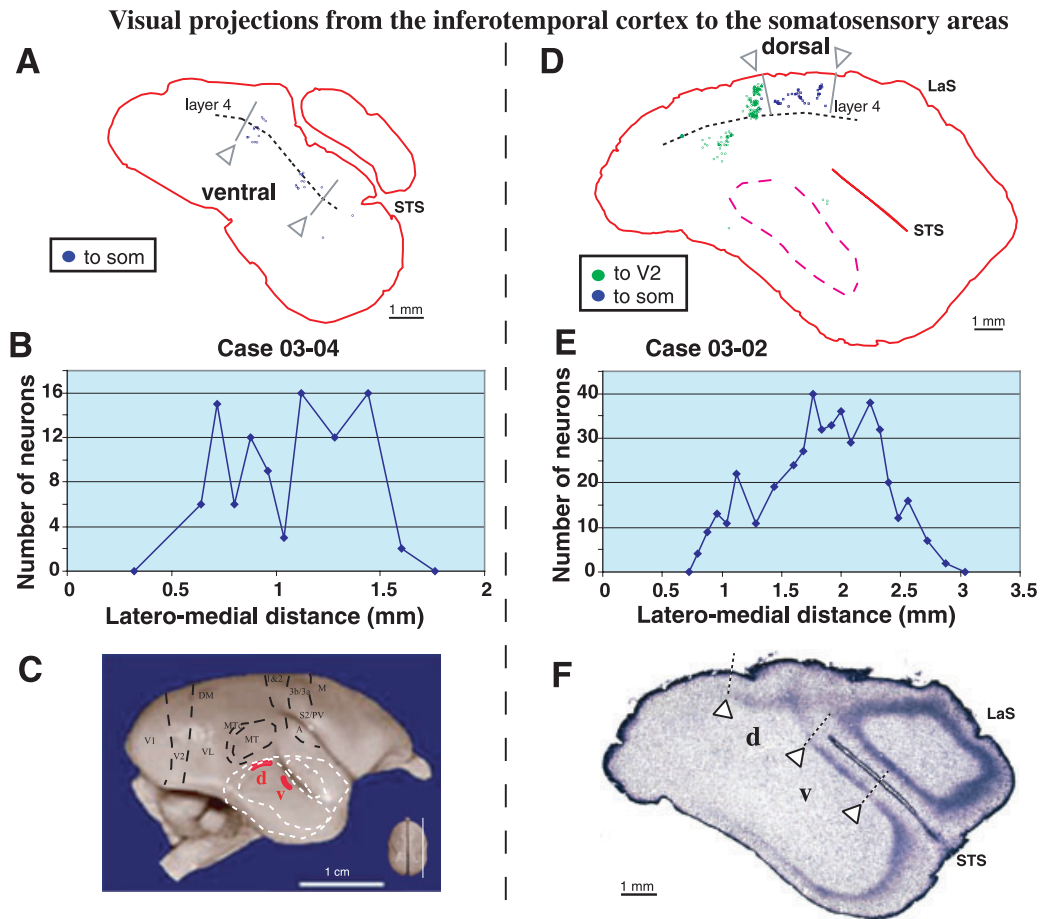

FIG. 5.

them involved the full depth of the cortex invading all six cortical layers. None of the injections invaded the white matter. In the marmoset, as in the macaque, the auditory cortex is composed of a core containing the primary auditory area, A1, which is surrounded by several different areas composing the auditory belt (Aitkin *et al.*, 1986, 1988; Morel & Kaas, 1992; Hackett *et al.*, 2001). In three of four cases, the injections were placed in the core of the auditory cortex (Fig. 2C). The limits of the core were obtained using NAP and CO histochemistry, as this region is characterized by a high level of activity of these enzymes (Hackett *et al.*, 2001; Fonta *et al.*, 2004). In one of the three cases (03–02), the injection spread slightly beyond the core limits; however, we estimated that 70% of the extent of the injection site was restricted to the core. In the fourth remaining case (02–14, Fig. 2A) the injection involved partly the core of the auditory cortex (45%) but extended caudally into the adjacent areas that might not be entirely auditory modality. In this case our analysis was restricted to regions sharing a common pattern of labelling with that obtained following an injection restricted to the core. In all cases, the thalamic labelling was located in the medial geniculate body, delimited by CO (Fig. 2D and E).

Somatosensory injections

We succeeded in injecting the somato-motor areas in three cases, all of them being restricted to the grey matter and involving all layers (Fig. 3). In two of the cases (03–02 and 03–04) the dyes were located principally in the somatosensory areas 3b and area 1. Several lines of evidence support this assignment to areas 1/3b. Our injections were always located at the level of (or anterior to) the LaS, none of them was posterior to this sulcus. This eliminates the possibility that our injections were located in the posterior parietal areas such as the somatosensory areas 5 or 7, which are located more caudally. Second, we have used previous cytoarchitecture used to define areal borders of somatosensory areas in the monkey (Jones *et al.*, 1978; Carlson *et al.*, 1986). The injections were less than 3 mm posterior to the border between area 3a and the motor cortex (Fig. 3B). The motor cortex is characterized by the lack of a distinct granular layer 4 and the presence of numerous large pyramidal cells in layer 5 (enlarged view in Fig. 3B). This differs from area 3a, posterior to the motor cortex, which possesses a thin layer 4 and a prominent layer 5. The boundary between 3a/3b is more difficult to assess (Carlson *et al.*, 1986), unless one is using horizontal plane of section (Padberg *et al.*, 2005). Observations from Nissl-stained sections suggest that our injections were posterior to the border between areas 3a and 3b, based on more densely packed layers 4 and 6 in 3b (Fig. 3B; Huffman & Krubitzer, 2001a). Finally, we have defined the border between areas 1 and 3b using CO labelling, which is more strongly expressed in 3b compared with the more posterior area 1 (Fig. 3C). Taken together, the evidence suggests that the two injections made in the somatosensory cortex were predominantly located in area 3b but with a significant invasion into the posterior area 1. These two injections differed in their latero-medial position corresponding to different parts of body representation (Krubitzer &

Kaas, 1990b; Huffman & Krubitzer, 2001a). Based on the somatopy described in the marmoset, we consider that the more lateral injection (case 03–04) was placed in a region corresponding to the face, while the more medial injection targeted the arm or hand representation. In case 02–18 the injection was located more rostrally, within the motor cortex. In all cases the thalamic labelling was restricted to the ventral lateral (VL) and ventral posterior lateral (VPL) nuclei, which project specifically toward the somatosensory and motor cortices (Krubitzer & Kaas, 1992; Huffman & Krubitzer, 2001b).

Visual cortex injections

In one case (03–04) we placed a FE injection in the MT visual area, which can be delimited by a characteristic high myelin content (Krubitzer & Kaas, 1990a; Lyon & Kaas, 2001). This is shown in Fig. 4, which represents the myelin pattern of the physically flattened hemisphere. The highly myelined zone contains the vast majority of callosal projecting cells, and corresponds to MT contralateral to the injection site. Furthermore, the presence of a large number of labelled cells in layer 4B of the ipsilateral lower bank of the calcarine sulcus (see Fig. 9A) combined with the absence of projecting neurons in opercular V1 indicate that our injection was restricted to the peripheral upper visual representation of MT. Two injections were made in the central representation of the extrastriate area V2 (cases 02–18 and 03–02) at the V1/V2 border as indicated by CO and NAP staining. The V2 injections provide labelling in visual areas V1 and extrastriate visual areas (Lyon & Kaas, 2001). We did not find any labelling in areas devoted to a sensory modality other than vision, in agreement with recent findings suggesting that crossmodal connections of area V2 might be restricted to its peripheral representation (Falchier & Kennedy, 2002). Consequently we only used the labelling resulting from these V2 injections to confirm the visual nature of the posterior areas that contain non-visual projecting neurons resulting from simultaneous injections in auditory and somatosensory areas.

General observations

In all cases we found labelled cells in areas that have been previously described as projecting to the core of the auditory cortex or to somatosensory areas 1/3b, MT or V2. For example, the injections in the different regions of the auditory cortex show the existence of common afferents from the auditory belt located in the cortex lateral to the LaS (Aitkin *et al.*, 1988). Furthermore, in agreement with previous results, we found projections arising from a dorsal region in the frontal cortex and from the cingulate cortex, especially in the case where the injection spread outside the auditory core. Injections in areas 1/3b resulted in labelling in areas known to be connected to the somatosensory cortex (Krubitzer & Kaas, 1990b), among them primary motor cortex, supplementary motor area (SMA) and the somatosensory area S2. Following the injection in MT, labelled neurons are found in previously reported areas such as V1, V2, fundus of the superior temporal (FST) or medial superior temporal (MST) areas (Krubitzer & Kaas, 1990a; Berezovskii & Born, 2000). Thus, the

Fig. 5. Visual projections to somatosensory cortex. (A–C) After an injection in the somatosensory area, labelled neurons are observed in the gyrus posterior to the STS in visual area of the ventral part of the inferotemporal cortex. (A) A representative section containing labelled neurons (blue dots) after a fluororuby (FR) injection in areas 1/3b. The majority (85%) of labelled neurons are in the infragranular layers that correspond to a FB projection. (B) Density profile of the visual projection toward the somatosensory cortex, which represents the number of labelled neurons in individual sections across the latero-medial dimension. (C) Schematic localization of the section illustrated in (A) and (D). (D) A second visual area, located dorsal to the STS, contains neurons projecting to the somatosensory areas 1 and 3b (blue dots). Most (84%) of labelled neurons are in the supragranular layers corresponding to a FF projection. Green dots are V2 projecting neurons. (E) Density profile of the dorsal projection to the somatosensory cortex. (F) Parasagittal section stained for NAP expression. NAP is strongly expressed in layer 4, especially in the ventral region (v) on the posterior bank of the STS. Based on the differential levels of NAP activity we have placed presumptive borders (white arrowheads and grey lines) between the two visual inferotemporal regions (d and v) that project toward the somatosensory cortex. The putative correspondence of these two regions with areas FSTd and FSTv is discussed (see Discussion).

connectivity pattern resulting from the individual injections agrees with earlier studies and provides evidence that our injection sites were restricted to areas of a single modality.

Heteromodal connections

In addition to the intramodal connectivity concerning the visual, auditory and somatosensory areas in which we placed our injections, we discovered other projections that link areas of different modalities. These heteromodal connections include visual to somatosensory, visual to auditory, as well as somatosensory to auditory. These observations were surprising in view of the supposed unimodal nature of the injected areas, the core of the auditory cortex, and areas 1 and 3b. Furthermore, by making simultaneous injections into different sensory cortices, we were able to locate polymodal areas that contained two or three types of labelled cells. All together these results provide novel information about the cortical network that might be involved in multisensory processing in the marmoset.

Visual projections to somatosensory cortex

Our results show the existence of direct projections from three visual areas to somatosensory cortex. First, following all injections in the somatosensory cortex, we observed labelled neurons in a temporal visual region located laterally and dorsally to the superior temporal sulcus (STS). Labelled cells in this mid-ventral temporal region were located in two spatially separate subregions (Fig. 5). One region containing labelled neurons was positioned at the tip of the STS, and the second one was situated at the caudal part of the posterior bank of the STS. In the absence of electrophysiological criteria to precisely identify these areas (see Discussion), we will refer to them as mid-ventral inferotemporal regions (MVIT), based solely on their location on the surface of the brain. However, we observed that NAP is differentially expressed in the dorsal and ventral regions, being stronger in the latter (Fig. 5F), suggesting that the dorsal and ventral regions might correspond to distinct cortical areas. The ventral region, located posterior to the STS, contains neurons projecting to the somatosensory cortex in both cases injected (Fig. 5A–C). The density curves of the ventral projections have a characteristic bell shape, indicating that the projection is topographically organized (Batardiere *et al.*, 1998; Barone *et al.*, 2000), but not of great magnitude. We found at most between 20 and 30 labelled neurons in individual sections, the higher density being observed following an injection in the hand/arm representation. In the two cases, in addition to labelled neurons projecting to the somatosensory cortex, the area contained labelled neurons following an injection of either V2 (foveal representation; 03–02) or MT (peripheral representation; 03–04), supporting the visual nature of this region. The projecting cells directed toward foveal V2 and areas 1/3b were mainly intermingled within the ventral region. Further, labelled neurons that belong to the ventral region projecting to peripheral MT are mainly segregated from the projection zone directed toward the face representation of areas 1/3b. This means that the projection zone in the ventral region targeting the somatosensory cortex is located in a foveal visual representation.

The second projection arising from the MVIT region was located immediately dorsal to the STS (Fig. 5D–F). We observed that this visual region projects quite strongly to the somatosensory cortex representing the arm/hand body part, and we counted close to 500 labelled cells in the entire projection zone. We did not observe such a projection from the dorsal region toward the face representation (case 03–04). When we made simultaneous injections in V2 and areas 1/3b, we observed that the two projection zones were overlapping, especially in the more medial sections containing both types of retrogradely labelled neurons (Fig. 6). Figure 6 illustrates the areal and density distribution of the V2 and somatosensory projections in the dorsal MVIT. It can be seen that the densities of the projections are similar in the two cases (about 500 labelled cells in the full projection zones). Further, the density profiles demonstrate that the two populations largely overlap, but the visual to somatosensory cortex projection is more broadly distributed in the latero-medial dimension. This suggests that the projection toward the somatosensory cortex might cover a large visual field representation or is loosely linked to the visual retinotopic organization of the dorsal mid-ventral temporal region.

Second, following an injection of tracer in MT, we observed, as reported earlier in the owl monkey (Kaas & Morel, 1993; Berezovskii & Born, 2000), a weak projection in the area posterior to MT on the convexity and defined as middle temporal crescent (MTc) in the marmoset (Rosa & Elston, 1998). The same area contains also, and in a higher density, labelled cells following injection in V2. This cortical area MTc also contains neurons projecting to the somatosensory cortex areas 1/3b (case 03–04, Fig. 7) representing the face. As previously noted for the other visuo-somatosensory connections, this projection was topographically organized and did not represent only randomly scattered projecting cells (Fig. 7C). No labelled neurons were observed in MTc when the somatosensory injection was made in the arm representation of areas 1/3b.

Finally, the mid-ventral temporal complex and area MTc did not contain any labelling following an injection restricted to the motor cortex (case 02–18). In addition, in regions containing two populations of projecting cells (to areas 1/3b and V2 or MT) we did not find double-labelled cells, suggesting the absence of bifurcating neurons projecting simultaneously toward two different sensory areas.

The laminar distribution of projecting neurons gives important information as to the *direction* of a projection between interconnected areas (Rockland & Pandya, 1979). A regular sampling analysis allowed us to compute the laminar origin of the visuo-somatosensory projections. We found that the projection from the more ventral inferotemporal region toward the somatosensory cortex (arm and face representations) is a feedback projection as in the two cases the majority of the labelled neurons were in the infragranular layer (%infra = 85%). On the contrary, the projections from both the dorsal MVIT and MTc directed to the somatosensory cortex (arm or face representation, respectively) correspond to a FF type of connection, because most of the projecting cells were in the upper laminar compartment (%supra = 84% and 99%, respectively).

Visual projections to auditory cortex

Injections of retrograde tracers in the core of the auditory cortex show the existence of a projection from a visual area located on the gyrus anterior to the STS (Fig. 8). In the latero-medial dimension, the extent of the projection zone extends from the very beginning of the STS to the beginning of the LaS (see Fig. 8C). To avoid inclusion of labelled neurons that could belong to auditory areas of the belt, we have restricted our counting to the more lateral sections, which we supposed to be of visual modality and probably homologous to superior temporal polysensory (STP) area of the macaque (see Discussion). This region contains neurons retrogradely labelled regardless of the exact position of the injection site in the auditory cortex (whether it involves predominantly the cortex inside or outside the core). This
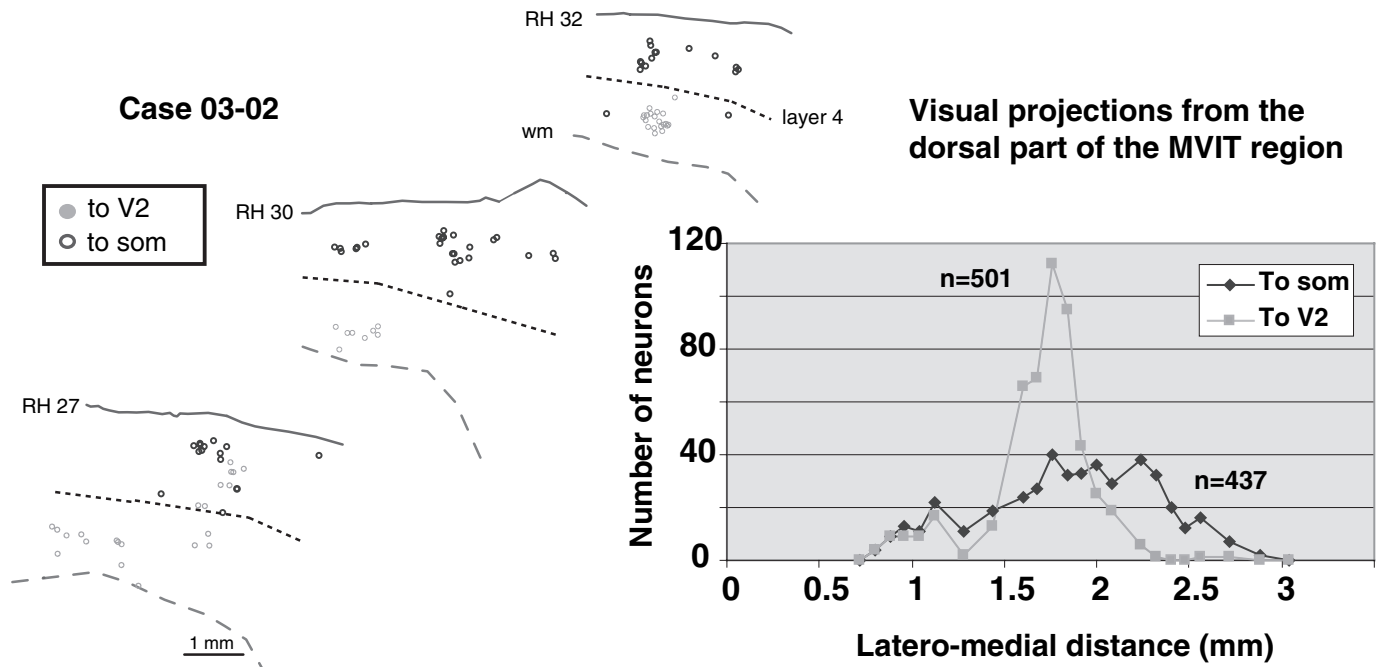
FIG. 6. Visual and somatosensory projections from area located in the dorsal part of the temporal cortex. Open dots represent labelled neurons following an injection in the somatosensory cortex and filled dots indicate V2 projecting neurons. The two populations are interleaved as seen on three successive sections. The right panel shows the density profiles of the two projections, which largely overlap in the latero-medial direction. The total number of labelled neurons is indicated. Conventions as in Fig. 5.
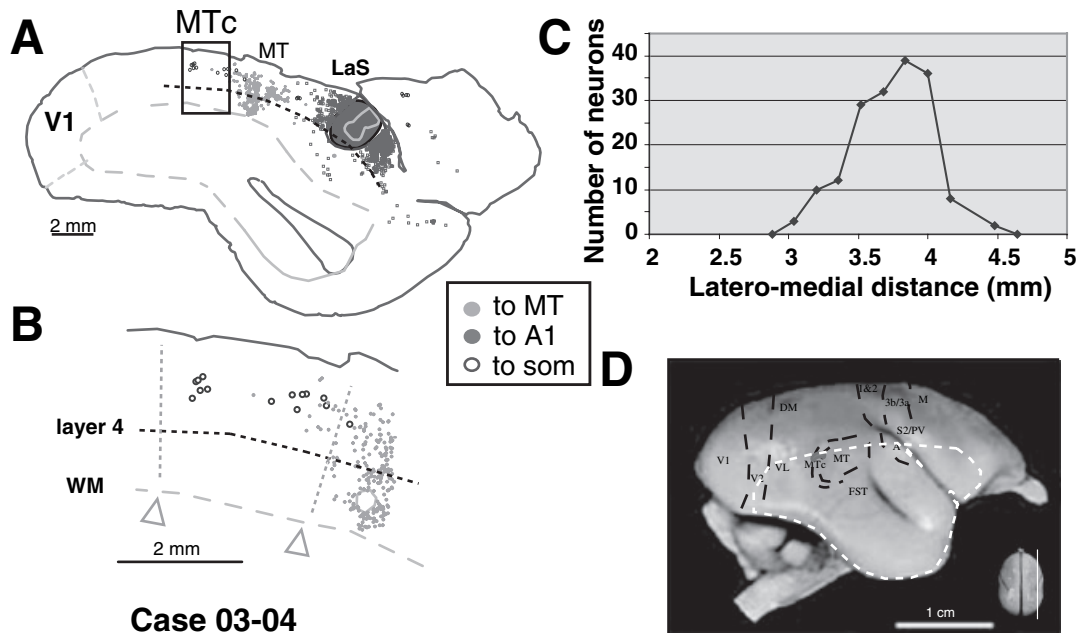

FIG. 7. (A) Following a Dyamidino-Yellow (DY) injection in areas 1 and 3b, we found a projection arising from area of the middle temporal crescent (MTc; indicated by the black square) located dorsal and caudal to area MT. Nearly all (99%) of labelled neurons are in the supragranular layers corresponding to a FF projection. The black drawing corresponds to a FR injection in the auditory core, and the high density of grey dots corresponds to the intrinsic labelling following an injection of fluoroemerald (FE) in MT. Note that the somatosensory region anterior to the lateral sulcus (LaS) contains neurons projecting (black dots) to the auditory core. (B) High-power view of the distribution of projecting neurons in MTc. (C) Density profile of the MTc projection toward the somatosensory cortex. (D) Localization of MTc represented on a schematic view of the brain. Conventions as in Fig. 5.

projection is quite significant as we found from 400 to nearly 1000 retrogradely labelled neurons on three–five successive sections. In the case involving predominantly the dorsal auditory belt (02–14), we found a higher density of labelled cells compared with that obtained following a core injection. The visual projection from the STS region to the auditory cortex is a FB projection, in all cases the majority of
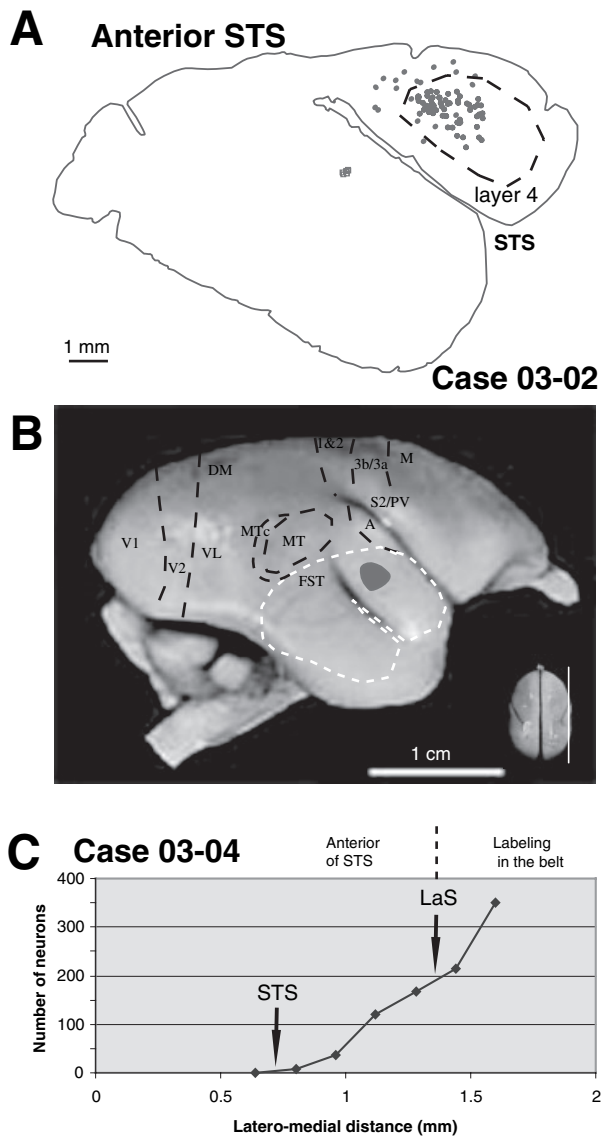
FIG. 8. (A) Distribution of labelled neurons in visual area anterior to the superior temporal sulcus (STS) following an injection of fluoroemerald (FE) in the core of the auditory cortex. Seventy-eight percent of labelled neurons are located in the infragranular layers corresponding to a FB projection. (B) Location of the illustrated section (dashed line) on a schematic view of the marmoset brain areas. The grey region corresponds to the region containing the labelled neurons. (C) Density profile of the projection toward the auditory cortex. In this graph two arrows indicate the apparition of the lateral sulcus (LaS) and STS on successive parasagittal sections. The labelling is observed at the most lateral section at the first appearance of the STS. We considered that the labelling at the level of the LaS belongs to auditory areas and was not considered in the counting. Conventions as in Fig. 5.

projecting cells are originating from the infragranular layers (mean percentage infra = 63%).

Somatosensory projections to auditory cortex

Following an injection of tracer in the core of the auditory cortex, we observed that most of the labelling was located in the posterior bank of the LaS and on the lateral convexity adjacent to the LaS. This corresponds to the known pattern of connectivity among auditory areas (Aitkin *et al.*, 1988; Hackett *et al.*, 1998a).

Furthermore, projection neurons were also present in the anterior bank of the LaS, especially following the more lateral injection in the core (03–04, see Figs 9A and 7A). While the functional modality of this cortical region has not been defined in the marmoset, we suggest that it might belong to somatosensory-related areas. In the New World owl and Titi monkeys (Cusick *et al.*, 1989; Coq *et al.*, 2004), the lower bank of the LaS, where we found labelled neurons, corresponds to the ventral somatosensory area (VS), which is bordered anteriorly by area S2. This is supported by the presence of labelled neurons projecting to the somatosensory areas 1/3b (Fig. 9A).

In addition, we found a second heteromodal connection following an injection into auditory cortex. We observed retrogradely labelled neurons in a region dorsal and anterior to the tip of the LaS (Fig. 9B) and probably corresponding to somatosensory area S2 (Krubitzer & Kaas, 1990b). Nissl staining clearly demonstrates that this area is posterior to the motor cortex. The labelling is clearly segregated from the isolated patch of auditory projection neurons in the anterior bank of the LaS. Furthermore, in the same case, area S2 contains cells labelled by an injection into areas 1/3b, but these auditory- and somatosensory-projecting patches are spatially segregated. The strongest density of the S2 projection to the auditory core was seen in the case (03–04) in which the auditory injection is more ventrally located. In this case, the density curve of the projection is clearly bell-shaped with a peak value of the number of labelled neurons greater than 30 (Fig. 9C). More posterior injections of dyes in the auditory cortex gave only scattered labelled neurons in S2. In all cases, all labelled neurons were in the infragranular layers (%infra = 100%), indicating a FB projection.

Multimodal areas

Multiple simultaneous injections in areas subserving different sensory modalities revealed marmoset cortical regions that can be defined as polymodal. The cortical region adjacent to the posterior tip of the LaS constitutes a real nexus of visual, auditory and somatosensory projections. For example, in case 03–04, in which we made simultaneous injections of dyes in MT, areas 1/3b and the auditory core, we found in this region a large population of intermingled labelled neurons (Fig. 10). In this case, there was a similar density of neurons projecting to each injected area. However, in other cases of concomitant injections in auditory and somatosensory cortices (02–18 and 03–02), the somatosensory injection always produced a higher density of labelled cells. We did not observe double-labelled neurons in this region. Of interest is that the laminar distribution differs according to the target area: projection to areas 1/3b involves mainly the supragranular layers, while the MT and auditory projections are of a feedback type.

The other cortical area that provides inputs to the three modalities is located in the frontal lobe on the dorsal convexity (Fig. 11). In cases of injections in area MT, areas 1/3b and the auditory core we observed retrogradely labelled neurons in a common cortical region. In all cases, the projection zones extended on a distance of 2–3 mm in the latero-medial direction and end up at about 3–4 mm from the medial edge of the brain. Only a few labelled neurons were present following an injection in the auditory core (Fig. 11C), but the frontal projection was much denser when the injection site involved predominantly the auditory belt (case 02–14, Fig. 11D and E). The frontal projection targeting areas MT and areas 1/3b (Fig. 11F–I) were of similar densities, and the projection zones involved in these connections showed a spatial overlap (see Fig. 11F). Concerning the laminar distribution of the individual projections, we found clear differences
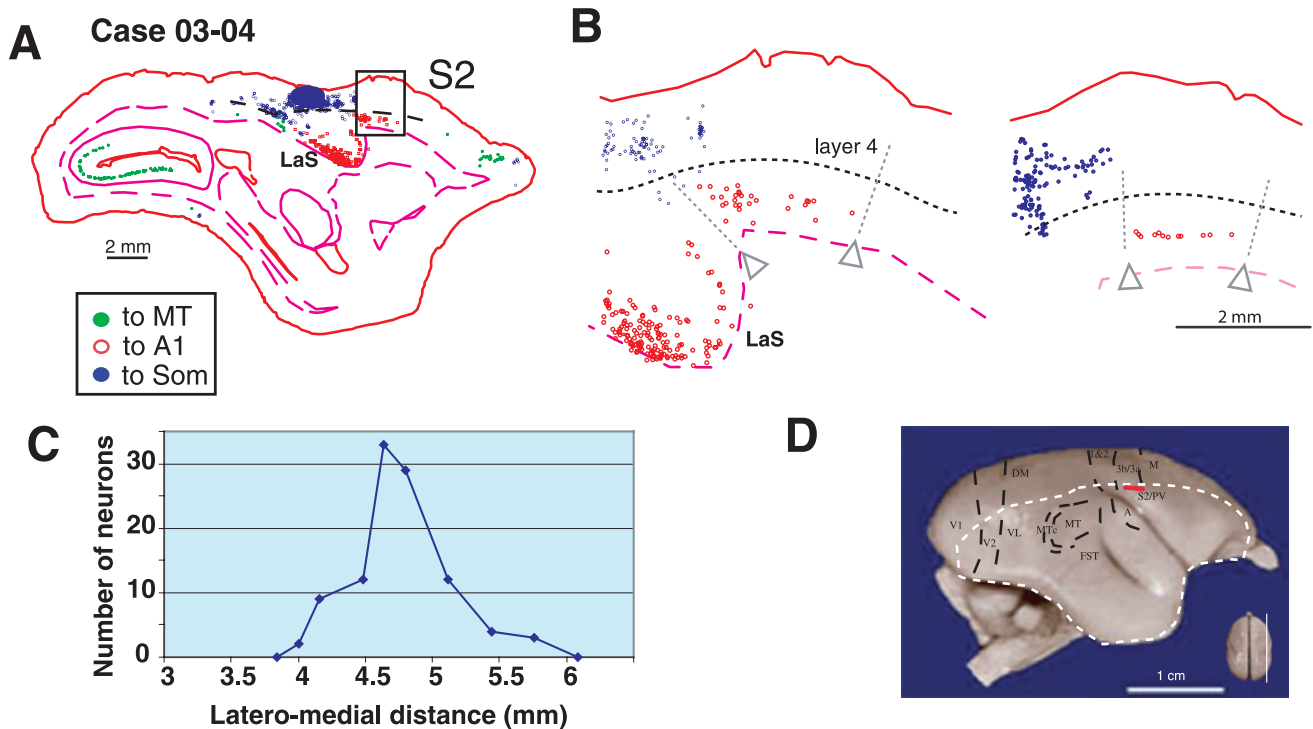
FIG. 9. (A) Retrogradely labelled neurons in the infragranular layers of the somatosensory area S2 (indicated by a square) following a fluororuby (FR) injection in auditory cortex. Green and blue dots represent labelled neurons following dye injections, respectively, in MT and areas 1/3b (filled blue region). Note the presence of labelled neurons in layer 4B of V1 along the calcarine sulcus. (B) High-power view of two parasagittal sections at the level of S2 showing retrogradely labelled neurons projecting to the auditory core. The S2 projection (located in between the grey arrowheads) is segregated from another somato-auditory projection originating from the anterior bank of the LaS that might correspond to area VS. (C) Density profile of the S2 projection toward the auditory cortex. (D) Localization of S2 represented on a schematic view on the brain. Conventions as in Fig. 5.
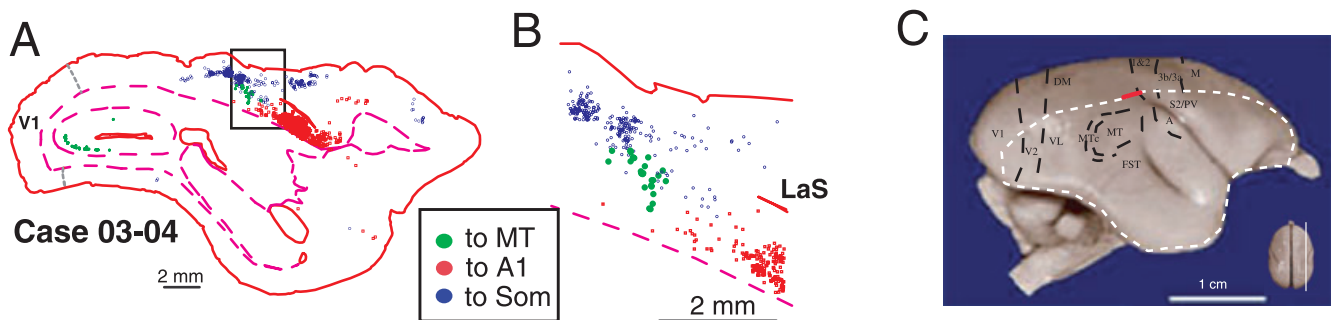

FIG. 10. On the posterior tip of the lateral sulcus (LaS), a temporal region (square region) projects simultaneously to the auditory (core), somatosensory (areas 1/3b) and visual cortices (MT), and could be defined as a multisensory node. (B) High-power view of a parasagittal section showing retrogradely labelled neurons projecting to MT (green), A1 (red) and S1 (blue). (C) A schematic view of the brain showing the location of the region that projects simultaneously to the three areas representing different sensory modalities. Conventions as in Fig. 5.

indicating opposite directions. In all cases the auditory projections originate from the lower layers (mean: 78% infragranular) characteristic of a FB projection, while the visual (to MT) and somatosensory (to areas 1/3b) projection neurons were in the supragranular layers (58 and 70% supragranular, respectively) defining FF connections.

Discussion

The aim of the present study was to search for connections that link cortical regions involved in processing information of different modalities. This was motivated by recent evidence in man of crossmodal interactions in sensory areas thought to be unimodal (see below; Schroeder & Foxe, 2004).

Injection sites

With our strategy of placing retrograde tracers in the auditory and somatosensory cortices, it was important to be sure that our dye injections were restricted to a single area or at least in areas dedicated to the processing of a single modality. This was only partially successfully done in cases of injections in the somatosensory cortex. Using anatomical criteria, we believe that our injection sites targeted principally area 3b, but also involved the posterior area 1. We also took care to verify that our injection sites did not involve more posterior areas such as area 5 or area 7b, because in the New World monkey these two parietal areas are connected with non-somatosensory areas and respond more-or-less predominantly to visual stimulation (Padberg et al., 2005). While electrophysiological criteria
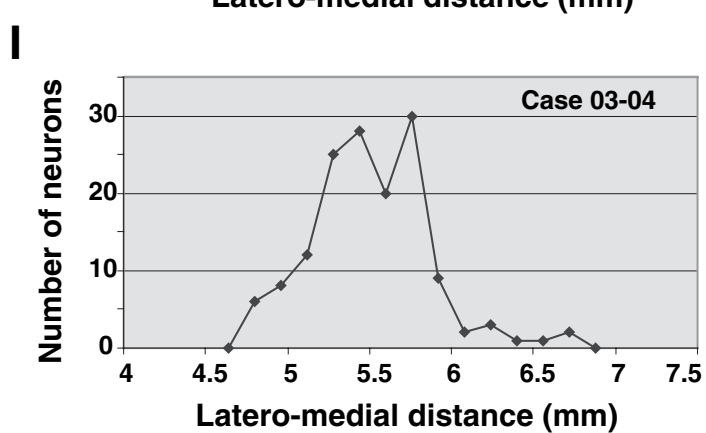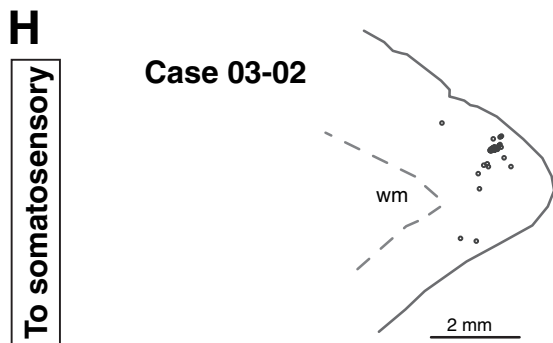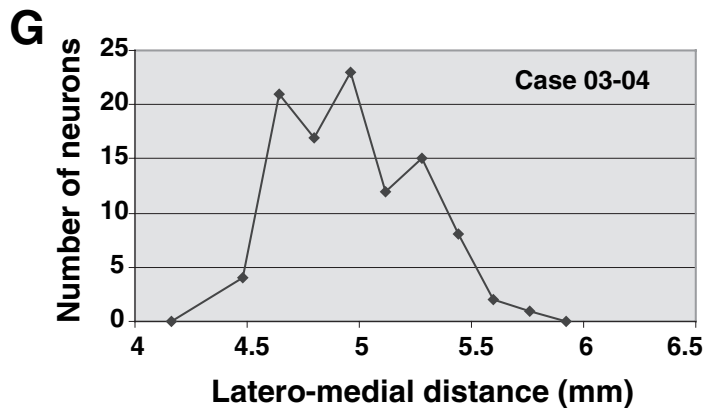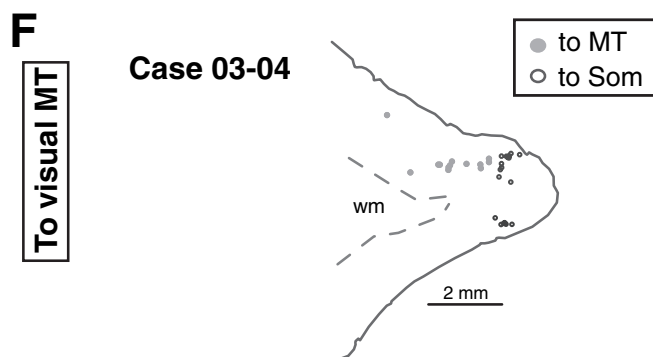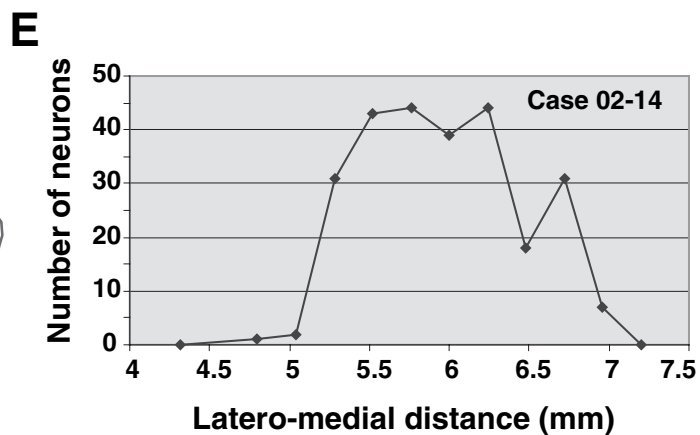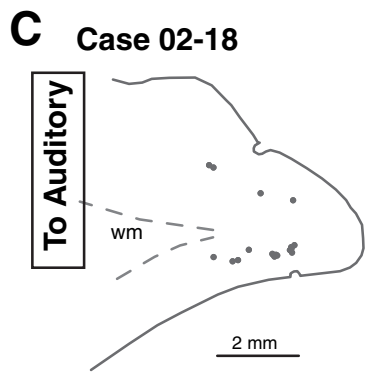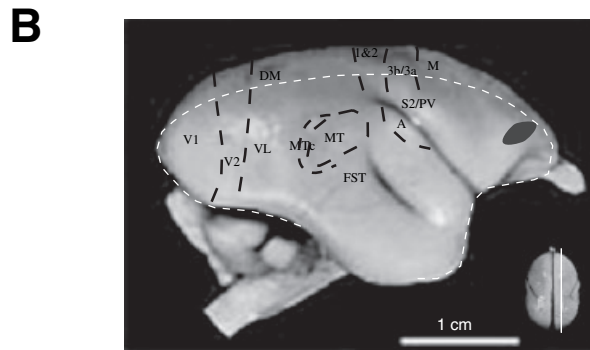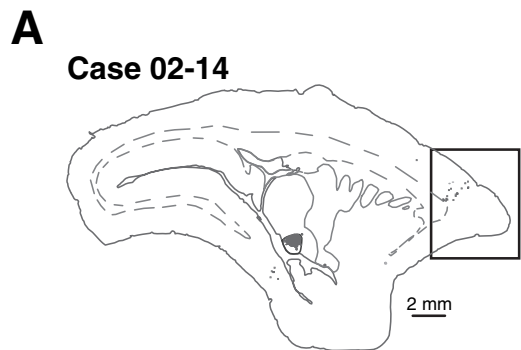
would provide the best evidence for the location of the injection site, we have indirect cues in favour of the injection sites not being localized to areas 5 or 7b. First, the thalamic labelling was restricted to the VP and VPL nuclei, suggesting that our injections were restricted to areas involved in somatosensory functions. We did not observe labelling in the lateral posterior pulvinar, which projects to more posterior parietal areas (Baleydier & Mauguiere, 1977; Acuna *et al.*, 1990), a multimodal region involved also in visual processing (Colby & Duhamel, 1991). Second, the cortical regions containing retrogradely labelled cells were observed in somatosensory-related areas such as S2, the primary (M1) and supplementary (SMA) motor areas, and few were located in the posterior parietal cortex (Krubitzer & Kaas, 1990b; Huffman & Krubitzer, 2001a). For example, area 7b received a strong projection from the auditory-related cortex (Padberg *et al.*, 2005), a connection we did not observe in our two cases. Lastly, we observed callosal projections originating only from a restricted region probably corresponding to the homotopic areas 1, 3b/3a (see Fig. 4B). In contrast, in the Titi monkey, callosal projections directed to areas 5 and 7b are more widespread across the cortex and involve, among others, the posterior parietal cortex as well as the cingulate cortex (Caminiti & Sbriccoli, 1985; Cavada & Goldman-Rakic, 1989; Padberg *et al.*, 2005). No such connections were observed in our two cases, suggesting that our injections did not involve areas 5 and 7b.

The location of the injections in the auditory cortex was assessed using multiple criteria (cortical and thalamic connectivity, cytoarchitecture). We used CO labelling to allocate areal borders because in the macaque (Morel *et al.*, 1993), A1 is characterized by a strong CO activity in layer 4. In only one case out of four did the injection site involve predominantly a cortical region outside the core of the auditory cortex. This case was excluded from the analysis of heteromodal connections as it presented a strong connectivity with parietal and inferotemporal visual cortex suggesting an involvement of non-auditory areas in the injection site (probably MST).

There are several reasons why previous studies may have failed to find such crossmodal connectivity (Kaas & Collins, 2004). One could be differences in the location of the injection sites, as we have observed that heteromodal connections can depend on the location within a corticotopic representation (see below). However, we believe a major reason is that in previous studies, attention was not focused on the issue of crossmodal interactions. We have discovered in published figures several examples of heteromodal connections that were not discussed in the main results. The aim of this study was to describe and quantify precisely these crossmodal connections.

Non-somatosensory inputs to areas 1 and 3b

Following injections of dyes in the somatosensory cortex (areas 1 and 3b), we found heteromodal inputs originating from areas known as visual. We report three distinct visual regions that project directly to areas 1/3b. First we observed labelled neurons in two subregions of the inferotemporal cortex located ventrally to area MT. Theses areas are probably visual based on the presence of retrogradely labelled neurons following paired injections in visual areas V2 or MT. We suggest that these two regions correspond to areas FSTv and FSTd (ventral and dorsal FST) described in the New World owl monkey

(Kaas & Morel, 1993; Berezovskii & Born, 2000). In agreement with these studies we observed that the two subdivisions send projections to V2 and MT but with a differential density, the one to V2 being weaker. In the marmoset, only the dorsal region (FSTd) has been clearly identified based on electrophysiological grounds (Rosa & Elston, 1998). In the absence of such criteria, we cannot rule out the possibility that the dorsal region projecting to areas 1 and 3b might correspond to the middle temporal crescent (MTc), which in the marmoset surrounds MT along its ventral border (Rosa & Elston, 1998).

None of these visual projections has been described previously to target area 3b in the marmoset or macaque monkey (Krubitzer & Kaas, 1990b; Darian-Smith *et al.*, 1993). However, a recent study mentions the presence of retrogradely labelled cells in the STS following an injection of tracers in area 1 of the Titi monkey (Padberg *et al.*, 2005). As our injection sites spread over area 1 it is possible that these visual projections are specific to area 1 but not 3b. In addition these visual projections target specific body representation in the somatosensory cortex. The face area receives inputs only from the ventral region, while the hand/arm representation receives inputs from the two visual regions. Further, the laminar patterns of projections from the ventral or dorsal regions to areas 1/3b are different: the ventral projection is of the FF pattern, whereas the one originating from the dorsal region is FB. On one hand, these results can give further support to the idea that FST region can be divided into two separate areas, namely FSTd and FSTv based on connectivity (Kaas & Morel, 1993; Stepniewska & Kaas, 1996; Berezovskii & Born, 2000) and modelling data (Hilgetag *et al.*, 1996). On the other hand, the different pattern of visual projections to the somatosensory cortex could be the consequence of the duality of our injection sites, which concern both areas 1 and 3b.

Area FST is defined as a visual area based on its connectivity pattern (Ungerleider & Desimone, 1986; Boussaoud *et al.*, 1990) and electrophysiology (Rosa & Elston, 1998). FST neurons in macaque respond to complex moving stimuli and have large receptive fields (Desimone & Ungerleider, 1986; Vanduffel *et al.*, 2001). To our knowledge neither anatomical nor electrophysiological studies have implicated the FST region in processing information other than visual. However, FST is interconnected with the posterior parietal cortex (Boussaoud *et al.*, 1990; Kaas & Morel, 1993; Lewis & Van Essen, 2000a), which contains multimodal neurons (Duhamel *et al.*, 1998; Bremmer *et al.*, 2002), a potential source of somatosensory inputs to this visual area. How these putative somatosensory inputs to FST are related to the projection from FST to areas 1/3b remains to be established. However, these visuo-somatosensory projections presently described could be the source of visual responses recently observed in the somatosensory area 1 of the Titi (Padberg *et al.*, 2005).

We found that visual area MTc projects to the face representation within somatosensory area 1/3b. We assigned this region to area MTc based on our observations of a dense projection from this area to V2 (case 03–02) and a weak one to MT (case 03–04) in agreement with previous results in the owl monkey (Kaas & Morel, 1993). While the homology of areas between the New and Old World monkeys is difficult to establish, MTc of the marmoset might include the area V4t described in the macaque (Desimone & Ungerleider, 1986; Kaas, 1997). The anatomical links of area MTc/V4t are poorly known,

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FIG. 11. (A) Parasagittal section showing the frontal region (black square) that projects to the auditory core, to area MT and to the somatosensory cortex and represented on a schematic view of the brain (B). (C–E) Frontal projection to the auditory core shown in two cases (C and D) and the corresponding density curve (E). (F) Location of frontal labelled neurons following a fluoroemerald (FE) injection in MT (filled dots) and the corresponding density curve (G). Note the presence in the same region of neurons projecting to the somatosensory cortex (open dots). (H) Parasagittal sections showing the location of neurons projecting to areas 1/3b (open dots). Note the correspondence in the location of the projection zone compared with the other case illustrated in (F). (I) Distribution of the number of projecting neurons along the latero-medial axis. Conventions as in Fig. 5.

beside its connections with the adjacent areas MT, FST, MST and V4 (Boussaoud *et al.*, 1990; Kaas & Morel, 1993; Barone *et al.*, 2000), suggesting that MTc is mainly involved in visual processing. None of these areas has been related to somatosensory processing, although some neurons in V4 have been reported to show tactile-related activity in the behaving monkey (Haenny *et al.*, 1988).

The visual inputs to areas 1/3b might be surprising, but close examination of the literature of the connectivity pattern of somatosensory cortex of the marmoset reveals the existence of projections from areas devoted to other modalities (Krubitzer & Kaas, 1990b; Huffman & Krubitzer, 2001a) and supports our present findings. For example, an injection of retrograde tracer in 3a produces labelling in a region just rostral to the FST complex (Krubitzer & Kaas, 1990b; Huffman & Krubitzer, 2001a), probably the visual area STP. Furthermore, area 3b also receives a weak projection from an area adjacent to the auditory field (Krubitzer & Kaas, 1990b). Though the nature of these projections was not discussed in the original papers, the cortical location of the areas projecting to 3a/3b make it likely that the somatosensory cortex is influenced by information from other sensory modalities.

Somatosensory and visual inputs to the auditory cortex

The auditory cortex in the marmoset is partly localized on the ventral surface of the LaS (Aitkin *et al.*, 1986; Kajikawa *et al.*, 2005), where we made our dye injections. Our data reveal two sources of somatosensory projections to the core of the auditory cortex, from the anterior bank of the LaS and from area S2. Previous studies of the connectivity of the New World (Aitkin *et al.*, 1988; Morel & Kaas, 1992) or Old World monkey auditory cortex (Morel *et al.*, 1993; Hackett *et al.*, 1998a) did not report such heteromodal connections. However, a S2 to A1 projection was illustrated in a study of the tamarin auditory cortex (Luethke *et al.*, 1989), a connection that might be reciprocal as it has been observed in the New World Titi monkey (Coq *et al.*, 2004). These observations combined with our own results are in agreement with electrophysiological recording in the macaque, showing somatosensory responses in the posterior auditory areas (Schroeder *et al.*, 2001, 2003). The short latencies of these responses suggest that they might be supported by direct inputs from S2. Furthermore, a ventral somatosensory region including S2, parietal ventral (PV) and area VS (Qi *et al.*, 2002) contains neurons that respond to auditory stimuli (Coq *et al.*, 2004), suggesting that these areas along with the posterior auditory fields belong to a larger cortical region involved in auditory and somatosensory integration.

In addition to somatosensory inputs, we observed that a visual area located anterior to the STS sends a projection to the auditory cortex. Based on its cortical location in the anterior bank of the STS, we suggest that this area could be the homologue of visual area STP described in the macaque (Cusick, 1997). In the macaque, STP is classified as a visual area (Felleman & Van Essen, 1991), but this cortical region is clearly multimodal as more than 50% of the visual neurons also respond to auditory or somatosensory stimuli (Desimone & Gross, 1979; Bruce *et al.*, 1981; Hikosaka *et al.*, 1988). However, anatomical studies in the macaque did not report such a projection from STP to the auditory core (Hackett *et al.*, 1998a), while in the owl monkey, the auditory cortex (core and belt) receives inputs from the supposedly visual superior temporal area (Morel & Kaas, 1992). Because in the marmoset the distance between the STS and the auditory areas around the LaS is reduced, only electrophysiological investigations can confirm our suggestion of a visual projection to the auditory core. Nevertheless, these visual projections might be the source of the visual responses observed in the auditory belt and core of the monkey (Schroeder & Foxe, 2002; Brosch & Scheich, 2005; Brosch *et al.*, 2005).

Polysensory areas in the marmoset

We observed a restricted region in the frontal lobe that projects simultaneously to the primary auditory and somatosensory cortices as well as to visual area MT. In the marmoset, two distinct frontal regions have been shown to project backward to sensory areas, the frontal eye field (FEF) and the frontal ventral area (FV). We were not able to distinguish these two regions, but the frontal projections to the auditory cortex apparently originated from two subregions. Nevertheless, our results suggest that the polymodal frontal region we labelled might correspond to area FV, because FV projects more strongly to area MT (Krubitzer & Kaas, 1990b) and to the auditory cortex (Morel & Kaas, 1992). While FV has been shown to be connected to the somatosensory areas PV and S2 (Krubitzer & Kaas, 1990b; Disbrow *et al.*, 2003), a direct projection to areas 1/3b has not been reported, probably because a frontal projection exists only for a particular body representation of the somatosensory cortex (see Huffman & Krubitzer, 2001a).

Lastly, our results suggest that the cortical region adjacent to the posterior tip of the LaS could be multisensory (Morel *et al.*, 1993), because it projects to the visual area MT and the auditory and somatosensory cortices. The definition of this region is still unknown. First, its cortical location suggests that it might correspond to the temporal opercular caudal cortex (Toc) described in the Macaque monkey (Lewis & Van Essen, 2000b), a region connected with the multisensory areas of the parietal cortex (Lewis & Van Essen, 2000a). Alternatively, this region might correspond to area MST, which in the New World monkey is located between MT and the LaS (Rosa & Elston, 1998; Berezovskii & Born, 2000). However, MST neurons are reported to be responsive only to visual stimuli (Desimone & Gross, 1979; Hikosaka *et al.*, 1988). Consequently, we cannot rule out the possibility that the region containing the three types of projections constitutes in fact the complex junction of three different areas of different modalities. However, as shown in Fig. 10, we observed a nice radial registration of the different labelled cells, suggesting that these neurons belong to a single area.

Direction of information flow across modalities

Connections that link cortical areas have been separated into two types, FF (or ascending) and FB (descending) according to the laminar pattern of cells of origin and axons terminals (Rockland & Pandya, 1979). FF projections originate predominantly from infragranular layers and target layer 4, while FB projections arise from infragranular layers and terminate outside layer 4. While the role of these two types of connections is only partially understood (Salin & Bullier, 1995; Bullier, 2003), the nature of the connections has been used to establish a hierarchical relationship between cortical areas (Maunsell & van Essen, 1983; Felleman & Van Essen, 1991) and thus to determine the direction of transfer of sensory information. By using a quantitative analysis of the laminar pattern of the projections (Barone *et al.*, 2000), we have shown that heteromodal connections can be of FB or FF types. We can rule out that the observed FF or FB patterns are dependent on the depth of injection in the target area. First, this parameter has no influence on the laminar pattern of retrograde labelling (Barone *et al.*, 1995; Batardiere *et al.*, 1998). Second, all our injections involve the full

thickness of the cortex; and third a single dye injection yields both FB and FF patterns of heteromodal connections (from the inferotemporal cortex to areas 1/3b, case 03–02).

From our data, no obvious general rules can predict the nature of the links between areas devoted to different modalities. For example, the projection from a visual to a somatosensory area can be FF or FB, and the auditory cortex receives only a FB type of heteromodal projection (from the visual area of the STS and somatosensory area S2). Similarly, electrophysiological recordings of multimodal responses have reported both types of influences (Foxe & Schroeder, 2005). Based on the laminar location of earliest activity, visual responses in the auditory cortex are located in supra- and infragranular layers, indicating a FB interaction (Schroeder & Foxe, 2002). On the other hand, initial somatosensory responses in the same auditory region are observed in layer 4, suggesting a FF influence (Schroeder *et al.*, 2001; Fu *et al.*, 2003).

In addition to the importance of these results concerning the hierarchical organization of information processing (see below), they raise the question of the applicability of the definition of FB and FF projections based on anatomical criteria when it involves connections that link areas of different modalities. The direct projection from the auditory cortex toward the visual area V1 is classified as FB because both the laminar location of projecting cells (Falchier *et al.*, 2002) and of terminals (Rockland & Ojima, 2003) correspond to the criteria of a FB definition. This could indicate that the previous anatomical definition of FB and FF connection applies to hetero-modal connections. However, our anatomical results are not in complete agreement with recent recordings in the auditory cortex, which suggest that somatosensory responses here result from a FF (Schroeder *et al.*, 2001; Fu *et al.*, 2003) or FB (Fu *et al.*, 2003) projection according to the type of stimulation. Our anatomical data indicate a FB source. Why such a discrepancy? First it could be because the source of the somatosensory responses recorded in the auditory cortex is not S2. An alternative pathway for multisensory integration at the cortical level could be through non-specific thalamic inputs (Cappe *et al.*, 2005) that can convey information from different modalities (see for review Schroeder & Foxe, 2005). Second, it is possible that the anatomical rules of FB/FF projections do not apply to heteromodal projections. One could imagine that the projection from S2 to the auditory cortex originates in infragranular layers (present study) and targets layer 4 (from electrophysiological data), i.e. an anatomical pattern combining FB and FF features.

Consequently, it could be that the functional distinction of cortical connections based solely on an anatomical definition does not apply when interactions between sensory modalities are involved and thus cannot be used to establish a functional hierarchy between areas of different systems. In support of this, recent analyses of cortico-cortical connections suggest that the anatomical pattern of projections depends on the intrinsic architecture of the interconnected areas in terms of laminar differentiation (Barbas & Rempel-Clower, 1997; Rempel-Clower & Barbas, 2000). How this rule of a structural dependency concerning the laminar organization of projections affects heteromodal connections remains to be determined.

In the frontal cortex we found that the projections to the posterior areas are of FB or FF direction, according to the modality of the target area. The projections toward a visual (MT) or somatosensory (1 and 3b) area are classified as FF, while the ones directed toward the auditory core are FB. This is in agreement with the anatomical data of the connectivity of the FEF (Vezoli *et al.*, 2004), a pattern that might depend either on the structural organization of the interconnected areas (Barbas, 1986) or on their hierarchical relationships (Felleman & Van Essen, 1991; Barone *et al.*, 2000).

Sensory representation and heteromodal connections

In the somatosensory system there is evidence for a different connectivity pattern according to the body representation, especially in terms of density of connections between areas (Krubitzer & Kaas, 1990b; Huffman & Krubitzer, 2001a). Similarly, in the visual system the density and laminar pattern of the links between visual areas also differ when they involve the central or peripheral visual field representation (Shipp & Zeki, 1989; Kaas & Morel, 1993; Schall *et al.*, 1995; Galletti *et al.*, 2001; Falchier *et al.*, 2002). Our present connectivity data show that the heteromodal connections might also be specific to the sensory representation. We found that the projections from the 'FST' complex are selective for the body part representation in areas 1/3b. As both injection sites involved two areas (area 1 and 3b) we cannot determine whether this reflects preferential connections to one or the other area. Similarly, auditory and multimodal projections to area V1 are restricted to the peripheral representation of the visual field (Falchier *et al.*, 2002). These results suggest that a primary sensory area, such as V1 or 3a/3b, is heterogeneous in terms of its areal connectivity, suggesting a regional functional specialization. The functional signification is unknown, but additional experiments would be interesting to check if the connectivity pattern is linked to the fact that the subdivisions of the FST complex belong to different functional visual streams. A specific link between the visual complex FST and the face representation in the somatosensory cortex could be involved in defensive or avoidance reflex as suggested by neuron properties in polysensory areas (Cooke & Graziano, 2003, 2004).

Multisensory integration at early stages

We have found several examples of direct connections between cortical areas involved in processing information of different modalities. More important, these heteromodal links concern auditory (core) and somatosensory areas (areas 1 and 3b), which are considered to belong to the first hierarchical levels in their respective modalities (Garraghty *et al.*, 1990; Hackett *et al.*, 1998b). These observations, in addition to previous findings of a direct link between primary visual and auditory cortices (Falchier *et al.*, 2002; Rockland & Ojima, 2003), suggest that multisensory interactions occur at early stages of information processing. In man and monkey, there is growing electrophysiological evidence of multi-modal interactions in areas known as unimodal (reviewed in Schroeder & Foxe, 2004). Visuo-auditory (Giard & Peronnet, 1999; Molholm *et al.*, 2002) or somato-auditory interactions (Foxe *et al.*, 2000; Murray *et al.*, 2005) occur in unimodal areas at very short latencies. Such a fast timing of multisensory interactions rules out an origin in the polymodal areas mediated through back projections, and instead favours direct heteromodal connections such as those we describe. The role of heteromodal connections is still poorly understood, but they are presumably directly involved in mecha-nisms of perceptual facilitation induced by bimodal stimulation (Giard & Peronnet, 1999; McDonald *et al.*, 2000; Lovelace *et al.*, 2003). However, the cortical network of multisensory integra-tion and the timing of crossmodal interactions probably depend on the nature of the task involved (Fort *et al.*, 2002; Wang *et al.*, 2005).

Furthermore, the existence of heteromodal connections at early stages of sensory processing has important consequences for under-standing functional reorganization following sensory deprivation. It is now well established that in the phenomenon of sensory substitution, the area involved in one modality can be functionally reoriented to

process another sensory modality (Bavelier & Neville, 2002; Roder & Rosler, 2004; Sathian, 2005). In congenital blindness the posterior visual areas can be activated by auditory or somatosensory stimuli (Kujala *et al.*, 1995; Sadato *et al.*, 1996; Weeks *et al.*, 2000; Roder *et al.*, 2002; Burton, 2003; Burton *et al.*, 2004) and, conversely, in deaf subjects the auditory areas can be driven by visual inputs (Finney *et al.*, 2001, 2003). While the pathways involved in this crossmodal plasticity are not fully understood (Pons, 1996; Theoret *et al.*, 2004), such mechanisms might be mediated through the direct heteromodal connections we have described.

Acknowledgements

Abbreviations

A1, primary auditory cortex; CO, cytochrome oxidase; FB, feedback; FEF, frontal eye field; FF, feedforward; FST, fundus of the superior temporal area; FSTd, dorsal FST; FSTv, ventral FST; FV, frontal ventral area; LaS, lateral sulcus; MST, medial superior temporal area; MT, middle temporal; MTC, middle temporal crescent; MVIT, mid-ventral inferotemporal regions; NAP, neuronal alkaline phosphatase; PV, parietal ventral somatosensory area; SMA, supplementary motor area; STP, superior temporal polysensory area; STS, superior temporal sulcus; VPL, ventral posterior lateral (nucleus); VS, ventral somatosensory area.

References

Acuna, C., Cudeiro, J., Gonzalez, F., Alonso, J.M. & Perez, R. (1990) Lateral-posterior and pulvinar reaching cells – comparison with parietal area 5a: a study in behaving Macaca nemestrina monkeys. *Exp. Brain Res.*, **82**, 158–166.

Aitkin, L.M., Kudo, M. & Irvine, D.R. (1988) Connections of the primary auditory cortex in the common marmoset, Callithrix jacchus jacchus. *J. Comp. Neurol.*, **269**, 235–248.

Aitkin, L.M., Merzenich, M.M., Irvine, D.R., Clarey, J.C. & Nelson, J.E. (1986) Frequency representation in auditory cortex of the common marmoset (Callithrix jacchus jacchus). *J. Comp. Neurol.*, **252**, 175–185.

Baleydier, C. & Mauguiere, F. (1977) Pulvinar-latero posterior afferents to cortical area 7 in monkeys demonstrated by horseradish peroxidase tracing technique. *Exp. Brain Res.*, **27**, 501–507.

Barbas, H. (1986) Pattern in the laminar origin of corticocortical connections. *J. Comp. Neurol.*, **252**, 415–422.

Barbas, H. & Rempel-Clower, N. (1997) Cortical structure predicts the pattern of corticocortical connections. *Cereb. Cortex*, **7**, 635–646.

Barone, P., Batardiere, A., Knoblauch, K. & Kennedy, H. (2000) Laminar distribution of neurons in extrastriate areas projecting to V1 and V4 correlates with the hierarchical rank and indicates the operation of a distance rule. *J. Neurosci.*, **20**, 3263–3281.

Barone, P., Dehay, C., Berland, M., Bullier, J. & Kennedy, H. (1995) Developmental remodeling of primate visual cortical pathways. *Cereb. Cortex*, **5**, 22–38.

Batardiere, A., Barone, P., Dehay, C. & Kennedy, H. (1998) Area-specific laminar distribution of cortical feedback neurons projecting to cat area 17: quantitative analysis in the adult and during ontogeny. *J. Comp. Neurol.*, **396**, 493–510.

Bavelier, D. & Neville, H.J. (2002) Cross-modal plasticity: where and how? *Nat. Rev. Neurosci.*, **3**, 443–452.

Baylis, G.C., Rolls, E.T. & Leonard, C.M. (1987) Functional subdivisions of the temporal lobe neocortex. *J. Neurosci.*, **7**, 330–342.

Berezovskii, V.K. & Born, R.T. (2000) Specificity of projections from wide-field and local motion-processing regions within the middle temporal visual area of the owl monkey. *J. Neurosci.*, **20**, 1157–1169.

Boussaoud, D., Ungerleider, L.G. & Desimone, R. (1990) Pathways for motion analysis: cortical connections of the medial superior temporal and fundus of the superior temporal visual areas in the macaque. *J. Comp. Neurol.*, **296**, 462–495.

Bremmer, F., Klam, F., Duhamel, J.R., Ben Hamed, S. & Graf, W. (2002) Visual-vestibular interactive responses in the macaque ventral intraparietal area (VIP). *Eur. J. Neurosci.*, **16**, 1569–1586.

Bremmer, F., Schlack, A., Shah, N.J., Zafiris, O., Kubischik, M., Hoffmann, K., Zilles, K. & Fink, G.R. (2001) Polymodal motion processing in posterior parietal and premotor cortex: a human fMRI study strongly implies equivalencies between humans and monkeys. *Neuron*, **29**, 287–296.

Brosch, M. & Scheich, H. (2005) Non-acoustic influence on neural activity in auditory cortex. In Kèonig, H. (Ed.), *The Auditory Cortex: a Synthesis of Human and Animal Research*. Lawrence Erlbaum, Mahwah, NJ, USA, pp. 127–144.

Brosch, M., Selezneva, E. & Scheich, H. (2005) Nonauditory events of a behavioral procedure activate auditory cortex of highly trained monkeys. *J. Neurosci.*, **25**, 6797–6806.

Bruce, C., Desimone, R. & Gross, C.G. (1981) Visual properties of neurons in a polysensory area in superior temporal sulcus of the macaque. *J. Neurophysiol.*, **46**, 369–384.

Bullier, J. (2003) Communications between cortical areas of the visual system. In Werner, J. & Chalupa, L. (Eds), *The Visual Neurosciences*. MIT Press, Cambridge, MA, pp. 522–540.

Burton, H. (2003) Visual cortex activity in early and late blind people. *J. Neurosci.*, **23**, 4005–4011.

Burton, H., Sinclair, R.J. & McLaren, D.G. (2004) Cortical activity to vibrotactile stimulation: an fMRI study in blind and sighted individuals. *Hum. Brain Mapp.*, **23**, 210–228.

Calvert, C.A., Brammer, M.J. & Iversen, S.D. (1998) Crossmodal identification. *Trends Cogn. Sci.*, **2**, 247–253.

Calvert, G.A., Campbell, R. & Brammer, M.J. (2000) Evidence from functional magnetic resonance imaging of crossmodal binding in the human heteromodal cortex. *Curr. Biol.*, **10**, 649–657.

Caminiti, R. & Sbriccoli, A. (1985) The callosal system of the superior parietal lobule in the monkey. *J. Comp. Neurol.*, **237**, 85–99.

Cappe, C., Barone, P. & Rouiller, E. (2005) Thalamocortical connectivity for multisensory and motor integration in the macaque monkey. *6th International Multisensory Research Forum*, Roveroto.

Carlson, M., Huerta, M.F., Cusick, C.G. & Kaas, J.H. (1986) Studies on the evolution of multiple somatosensory representations in primates: the organization of anterior parietal cortex in the New World Callitrichid, Saguinus. *J. Comp. Neurol.*, **246**, 409–426.

Cavada, C. & Goldman-Rakic, P.S. (1989) Posterior parietal cortex in rhesus monkey. I. Parcellation of areas based on distinctive limbic and sensory corticocortical connections. *J. Comp. Neurol.*, **287**, 393–421.

Colby, C.L. & Duhamel, J.R. (1991) Heterogeneity of extrastriate visual areas and multiple parietal areas in the macaque monkey. *Neuropsychologia*, **29**, 517–537.

Cooke, D.F. & Graziano, M.S. (2003) Defensive movements evoked by air puff in monkeys. *J. Neurophysiol.*, **90**, 3317–3329.

Cooke, D.F. & Graziano, M.S. (2004) Sensorimotor integration in the precentral gyrus: polysensory neurons and defensive movements. *J. Neurophysiol.*, **91**, 1648–1660.

Coq, J.O., Qi, H., Collins, C.E. & Kaas, J.H. (2004) Anatomical and functional organization of somatosensory areas of the lateral fissure of the New World titi monkey (Callicebus moloch). *J. Comp. Neurol.*, **476**, 363–387.

Cusick, C.G. (1997) The superior temporal polysensory region in monkeys. In Rockland, K.S., Kaas, J.H. & Peters, A. (Eds), *Cerebral Cortex*. Plenum Press, New York, pp. 435–468.

Cusick, C.G., Wall, J.T., Felleman, D.J. & Kaas, J.H. (1989) Somatotopic organization of the lateral sulcus of owl monkeys: area 3b, S-II, and a ventral somatosensory area. *J. Comp. Neurol.*, **282**, 169–190.

Darian-Smith, C., Darian-Smith, I., Burman, K. & Ratcliffe, N. (1993) Ipsilateral cortical projections to areas 3a, 3b, and 4 in the macaque monkey. *J. Comp. Neurol.*, **335**, 200–213.

Desimone, R. & Gross, C.G. (1979) Visual areas in the temporal cortex of the macaque. *Brain Res.*, **178**, 363–380.

Desimone, R. & Ungerleider, L.G. (1986) Multiple visual areas in the caudal superior temporal sulcus of the macaque. *J. Comp. Neurol.*, **248**, 164–189.

Disbrow, E., Litinas, E., Recanzone, G.H., Padberg, J. & Krubitzer, L. (2003) Cortical connections of the second somatosensory area and the parietal ventral area in macaque monkeys. *J. Comp. Neurol.*, **462**, 382–399.

Downar, J., Crawley, A.P., Mikulis, D.J. & Davis, K.D. (2000) A multimodal cortical network for the detection of changes in the sensory environment. *Nat. Neurosci.*, **3**, 277–283.

Dufour, A. (1999) Importance of attentional mechanisms in audiovisual links. *Exp. Brain Res.*, **126**, 215–222.

Duhamel, J.R., Colby, C.L. & Goldberg, M.E. (1998) Ventral intraparietal area of the macaque: congruent visual and somatic response properties. *J. Neurophysiol.*, **79**, 126–136.

Falchier, A., Clavagnier, S., Barone, P. & Kennedy, H. (2002) Anatomical evidence of multimodal integration in primate striate cortex. *J. Neurosci.*, **22**, 5749–5759.

Falchier, A. & Kennedy, H. (2002) Connectivity of areas V1 and V2 in the monkey is profoundly influenced by eccentricity. *FENS Forum*, Paris, pp. A051.058.

Felleman, D.J. & Van Essen, D.C. (1991) Distributed hierarchical processing in the primate cerebral cortex. *Cereb. Cortex*, **1**, 1–47.

Finney, E.M., Clementz, B.A., Hickok, G. & Dobkins, K.R. (2003) Visual stimuli activate auditory cortex in deaf subjects: evidence from MEG. *Neuroreport*, **14**, 1425–1427.

Finney, E.M., Fine, I. & Dobkins, K.R. (2001) Visual stimuli activate auditory cortex in the deaf. *Nat. Neurosci.*, **4**, 1171–1173.

Fonta, C., Négyessy, L., Renaud, L. & Barone, P. (2004) Areal and subcellular localization of the ubiquitous alkaline phosphatase in the primate cerebral cortex: evidence for a role in neurotransmission. *Cereb. Cortex*, **14**, 595–609.

Fonta, C., Negyessy, L., Renaud, L. & Barone, P. (2005) Postnatal development of alkaline phosphatase activity correlates with the maturation of neurotransmission in the cerebral cortex. *J. Comp. Neurol.*, **486**, 179–196.

Fort, A., Delpuech, C., Pernier, J. & Giard, M.H. (2002) Dynamics of cortico-subcortical cross-modal operations involved in audio-visual object detection in humans. *Cereb. Cortex*, **12**, 1031–1039.

Foxe, J.J., Morocz, I.A., Murray, M.M., Higgins, B.A., Javitt, D.C. & Schroeder, C.E. (2000) Multisensory auditory–somatosensory interactions in early cortical processing revealed by high-density electrical mapping. *Brain Res. Cogn. Brain Res.*, **10**, 77–83.

Foxe, J.J. & Schroeder, C.E. (2005) The case for feedforward multisensory convergence during early cortical processing. *Neuroreport*, **16**, 419–423.

Frens, M.A. & Van Opstal, A.J. (1995) A quantitative study of auditory-evoked saccadic eye movements in two dimensions. *Exp. Brain Res.*, **107**, 103–117.

Fu, K.M., Johnston, T.A., Shah, A.S., Arnold, L., Smiley, J., Hackett, T.A., Garraghty, P.E. & Schroeder, C.E. (2003) Auditory cortical neurons respond to somatosensory stimulation. *J. Neurosci.*, **23**, 7510–7515.

Galletti, C., Gamberini, M., Kutz, D.F., Fattori, P., Luppino, G. & Matelli, M. (2001) The cortical connections of area V6: an occipito-parietal network processing visual information. *Eur. J. Neurosci.*, **13**, 1572–1588.

Gallyas, F. (1979) Silver staining of myelin by means of physical development. *Neurol. Res.*, **1**, 203–209.

Garraghty, P.E., Florence, S.L. & Kaas, J.H. (1990) Ablations of areas 3a and 3b of monkey somatosensory cortex abolish cutaneous responsivity in area 1. *Brain Res.*, **528**, 165–169.

Giard, M.H. & Peronnet, F. (1999) Auditory-visual integration during multimodal object recognition in humans: a behavioral and electrophysiological study. *J. Cogn. Neurosci.*, **11**, 473–490.

Goldring, J.E., Dorris, M.C., Corneil, B.D., Ballantyne, P.A. & Munoz, D.P. (1996) Combined eye-head gaze shifts to visual and auditory targets in humans. *Exp. Brain Res.*, **111**, 68–78.

Graziano, M.S. (2001) A system of multimodal areas in the primate brain. *Neuron*, **29**, 4–6.

Guest, S., Catmur, C., Lloyd, D. & Spence, C. (2002) Audiotactile interactions in roughness perception. *Exp. Brain Res.*, **146**, 161–171.

Guest, S. & Spence, C. (2003) What role does multisensory integration play in the visuotactile perception of texture? *Int. J. Psychophysiol.*, **50**, 63–80.

Hackett, T.A., Preuss, T.M. & Kaas, J.H. (2001) Architectonic identification of the core region in auditory cortex of macaques, chimpanzees, and humans. *J. Comp. Neurol.*, **441**, 197–222.

Hackett, T.A., Stepniewska, I. & Kaas, J.H. (1998a) Subdivisions of auditory cortex and ipsilateral cortical connections of the parabelt auditory cortex in macaque monkeys. *J. Comp. Neurol.*, **394**, 475–495.

Hackett, T.A., Stepniewska, I. & Kaas, J.H. (1998b) Thalamocortical connections of the parabelt auditory cortex in macaque monkeys. *J. Comp. Neurol.*, **400**, 271–286.

Haenny, P.E., Maunsell, J.H. & Schiller, P.H. (1988) State dependent activity in monkey visual cortex. II. Retinal and extraretinal factors in V4. *Exp. Brain Res.*, **69**, 245–259.

Hikosaka, K., Iwai, E., Saito, H. & Tanaka, K. (1988) Polysensory properties of neurons in the anterior bank of the caudal superior temporal sulcus of the macaque monkey. *J. Neurophysiol.*, **60**, 1615–1637.

Hilgetag, C.C. & Grant, S. (2001) Uniformity and specificity of long-range corticocortical connections in the visual cortex of the cat. *Neurocomputing*, **38–40**, 667–676.

Hilgetag, C.C., O'Neill, M.A. & Young, M.P. (1996) Indeterminate organization of the visual system. *Science*, **271**, 776–777.

Huffman, K.J. & Krubitzer, L. (2001a) Area 3a: topographic organization and cortical connections in marmoset monkeys. *Cereb. Cortex*, **11**, 849–867.

Huffman, K.J. & Krubitzer, L. (2001b) Thalamo-cortical connections of areas 3a and M1 in marmoset monkeys. *J. Comp. Neurol.*, **435**, 291–310.

Jones, E.G., Coulter, J.D. & Hendry, S.H. (1978) Intracortical connectivity of architectonic fields in the somatic sensory, motor and parietal cortex of monkeys. *J. Comp. Neurol.*, **181**, 291–347.

Kaas, J. (1997) Theories of visual cortex organization in primates. In Rockland, K.S., Kaas, J. & Peters, A. (Eds), *Cerebral Cortex*. Plenum Press, New York, pp. 91–125.

Kaas, J. & Collins, C.E. (2004) The resurrection of multisensory cortex in primates: connection patterns that integrates modalities. In Calvert, G., Spence, C. & Stein, B.E. (Eds), *The Handbook of Multisensory Processes*. MIT Press, Cambridge, MA, pp. 285–293.

Kaas, J.H. & Morel, A. (1993) Connections of visual areas of the upper temporal lobe of owl monkeys: the MT crescent and dorsal and ventral subdivisions of FST. *J. Neurosci.*, **13**, 534–546.

Kajikawa, Y., de La Mothe, L., Blumell, S. & Hackett, T.A. (2005) A comparison of neuron response properties in areas A1 and CM of the marmoset monkey auditory cortex: tones and broadband noise. *J. Neurophysiol.*, **93**, 22–34.

Krubitzer, L.A. & Kaas, J.H. (1990a) Cortical connections of MT in four species of primates: areal, modular, and retinotopic patterns. *Vis. Neurosci.*, **5**, 165–204.

Krubitzer, L.A. & Kaas, J.H. (1990b) The organization and connections of somatosensory cortex in marmosets. *J. Neurosci.*, **10**, 952–974.

Krubitzer, L.A. & Kaas, J.H. (1992) The somatosensory thalamus of monkeys: cortical connections and a redefinition of nuclei in marmosets. *J. Comp. Neurol.*, **319**, 123–140.

Kujala, T., Alho, K., Kekoni, J., Hamalainen, H., Reinikainen, K., Salonen, O., Standertskjold-Nordenstam, C.G. & Naatanen, R. (1995) Auditory and somatosensory event-related brain potentials in early blind humans. *Exp. Brain Res.*, **104**, 519–526.

Laurienti, P.J., Burdette, J.H., Wallace, M.T., Yen, Y.F., Field, A.S. & Stein, B.E. (2002) Deactivation of sensory-specific cortex by cross-modal stimuli. *J. Cogn. Neurosci.*, **14**, 420–429.

Lewis, J.W. & Van Essen, D.C. (2000a) Corticocortical connections of visual, sensorimotor, and multimodal processing areas in the parietal lobe of the macaque monkey. *J. Comp. Neurol.*, **428**, 112–137.

Lewis, J.W. & Van Essen, D.C. (2000b) Mapping of architectonic subdivisions in the macaque monkey, with emphasis on parieto-occipital cortex. *J. Comp. Neurol.*, **428**, 79–111.

Lovelace, C.T., Stein, B.E. & Wallace, M.T. (2003) An irrelevant light enhances auditory detection in humans: a psychophysical analysis of multisensory integration in stimulus detection. *Brain Res. Cogn. Brain Res.*, **17**, 447–453.

Luethke, L.E., Krubitzer, L.A. & Kaas, J.H. (1989) Connections of primary auditory cortex in the New World monkey, Saguinus. *J. Comp. Neurol.*, **285**, 487–513.

Lyon, D.C. & Kaas, J.H. (2001) Connectional and architectonic evidence for dorsal and ventral V3, and dorsomedial area in marmoset monkeys. *J. Neurosci.*, **21**, 249–261.

Maeda, F., Kanai, R. & Shimojo, S. (2004) Changing pitch induced visual motion illusion. *Curr. Biol.*, **14**, R990–R991.

Maunsell, J.H. & van Essen, D.C. (1983) The connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey. *J. Neurosci.*, **3**, 2563–2586.

McDonald, J.J., Teder-Salejarvi, W.A. & Hillyard, S.A. (2000) Involuntary orienting to sound improves visual perception. *Nature*, **407**, 906–908.

McGurk, H. & MacDonald, J. (1976) Hearing lips and seeing voices. *Nature*, **264**, 746–748.

Meredith, M.A. & Stein, B.E. (1983) Interactions among converging sensory inputs in the superior colliculus. *Science*, **221**, 389–391.

Mistlin, A.J. & Perrett, D.I. (1990) Visual and somatosensory processing in the macaque temporal cortex: the role of 'expectation'. *Exp. Brain Res.*, **82**, 437–450.

Molholm, S., Ritter, W., Murray, M.M., Javitt, D.C., Schroeder, C.E. & Foxe, J.J. (2002) Multisensory auditory–visual interactions during early sensory processing in humans: a high-density electrical mapping study. *Brain Res. Cogn. Brain Res.*, **14**, 115–128.

Morel, A., Garraghty, P.E. & Kaas, J.H. (1993) Tonotopic organization, architectonic fields, and connections of auditory cortex in macaque monkeys. *J. Comp. Neurol.*, **335**, 437–459.

Morel, A. & Kaas, J.H. (1992) Subdivisions and connections of auditory cortex in owl monkeys. *J. Comp. Neurol.*, **318**, 27–63.

Murray, M.M., Molholm, S., Michel, C.M., Heslenfeld, D.J., Ritter, W., Javitt, D.C., Schroeder, C.E. & Foxe, J.J. (2005) Grabbing your ear: rapid auditory–somatosensory multisensory interactions in low-level sensory cortices are not constrained by stimulus alignment. *Cereb. Cortex*, **15**, 963–974.

Padberg, J., Disbrow, E. & Krubitzer, L. (2005) The organization and connections of anterior and posterior parietal cortex in Titi monkeys: do New World monkeys have an area 2? *Cereb. Cortex*, in press. [doi: 10.1093/Cercor/bhio71]

Pons, T. (1996) Novel sensations in the congenitally blind. *Nature*, **380**, 479–480.

Qi, H.X., Lyon, D.C. & Kaas, J.H. (2002) Cortical and thalamic connections of the parietal ventral somatosensory area in marmoset monkeys (Callithrix jacchus). *J. Comp. Neurol.*, **443**, 168–182.

Rempel-Clower, N.L. & Barbas, H. (2000) The laminar pattern of connections between prefrontal and anterior temporal cortices in the Rhesus monkey is related to cortical structure and function. *Cereb. Cortex*, **10**, 851–865.

Rockland, K.S. & Ojima, H. (2003) Multisensory convergence in calcarine visual areas in macaque monkey. *Int. J. Psychophysiol.*, **50**, 19–26.

Rockland, K.S. & Pandya, D.N. (1979) Laminar origins and terminations of cortical connections of the occipital lobe in the rhesus monkey. *Brain Res.*, **179**, 3–20.

Roder, B. & Rosler, F. (2004) Compensatory plasticity as a consequence of sensory loss. In Calvert, G., Spence, C. & Stein, B.E. (Eds), *The Handbook of Multisensory Processes*. MIT Press, Cambridge, MA, pp. 719–747.

Roder, B., Stock, O., Bien, S., Neville, H. & Rosler, F. (2002) Speech processing activates visual cortex in congenitally blind humans. *Eur. J. Neurosci.*, **16**, 930–936.

Rosa, M.G. (1997) Visuotopic organization of primate extrastriate cortex. In Rockland, K.S., Kaas, J.H. & Peters, A. (Eds), *Cerebral Cortex*. Plenum, New York, pp. 127–201.

Rosa, M.G. & Elston, G.N. (1998) Visuotopic organisation and neuronal response selectivity for direction of motion in visual areas of the caudal temporal lobe of the marmoset monkey (Callithrix jacchus): middle temporal area, middle temporal crescent, and surrounding cortex. *J. Comp. Neurol.*, **393**, 505–527.

Rosa, M.G. & Tweedale, R. (2000) Visual areas in lateral and ventral extrastriate cortices of the marmoset monkey. *J. Comp. Neurol.*, **422**, 621–651.

Rosa, M.G., Palmer, S.M., Gamberini, M., Tweedale, R., Pinon, M.C. & Bourne, J.A. (2005) Resolving the organization of the New World monkey third visual complex: the dorsal extrastriate cortex of the marmoset (Callithrix jacchus). *J. Comp. Neurol.*, **483**, 164–191.

Sadato, N., Pascual-Leone, A., Grafman, J., Ibanez, V., Deiber, M.P., Dold, G. & Hallett, M. (1996) Activation of the primary visual cortex by Braille reading in blind subjects. *Nature*, **380**, 526–528.

Salin, P.A. & Bullier, J. (1995) Corticocortical connections in the visual system structure and function. *Physiol. Rev.*, **75**, 107–154.

Sathian, K. (2005) Visual cortical activity during tactile perception in the sighted and the visually deprived. *Dev. Psychobiol.*, **46**, 279–286.

Sathian, K., Zangaladze, A., Hoffman, J.M. & Grafton, S.T. (1997) Feeling with the mind's eye. *Neuroreport*, **8**, 3877–3881.

Schall, J.D., Morel, A., King, D.J. & Bullier, J. (1995) Topography of visual cortex connections with frontal eye field in macaque: convergence and segregation of processing streams. *J. Neurosci.*, **15**, 4464–4487.

Schroeder, C.E. & Foxe, J.J. (2002) The timing and laminar profile of converging inputs to multisensory areas of the macaque neocortex. *Brain Res. Cogn. Brain Res.*, **14**, 187–198.

Schroeder, C.E. & Foxe, J.J. (2004) Multisensory convergence in early cortical processing. In Calvert, G., Spence, C. & Stein, B.E. (Eds), *The Handbook of Multisensory Processes*. MIT Press, Cambridge, MA, pp. 295–309.

Schroeder, C.E. & Foxe, J. (2005) Multisensory contributions to low-level, 'unisensory' processing. *Curr. Opin. Neurobiol.*, **15**, 454–458.

Schroeder, C.E., Lindsley, R.W., Specht, C., Marcovici, A., Smiley, J.F. & Javitt, D.C. (2001) Somatosensory input to auditory association cortex in the macaque monkey. *J. Neurophysiol.*, **85**, 1322–1327.

Schroeder, C.E., Smiley, J., Fu, K.G., McGinnis, T., O'Connell, M.N. & Hackett, T.A. (2003) Anatomical mechanisms and functional implications of multisensory convergence in early cortical processing. *Int. J. Psychophysiol.*, **50**, 5–17.

Shams, L., Kamitani, Y. & Shimojo, S. (2000) Illusions. What you see is what you hear. *Nature*, **408**, 788.

Shipp, S. & Zeki, S. (1989) The organization of connections between areas V5 and V1 in macaque monkey visual cortex. *Eur. J. Neurosci.*, **1**, 309–332.

Slutsky, D.A. & Recanzone, G.H. (2001) Temporal and spatial dependency of the ventriloquism effect. *Neuroreport*, **12**, 7–10.

Spence, C. & Driver, J. (2000) Attracting attention to the illusory location of a sound: reflexive crossmodal orienting and ventriloquism. *Neuroreport*, **11**, 2057–2061.

Spence, C. & Driver, J. (2004) Exogenous spacial-cueing studies of human crossmodal attention and multisensory integration. In Spence, C. & Driver, J. (Eds), *Crossmodal Space and Crossmodal Attention*. Oxford University Press, Oxford.

Stein, B.E. (1998) Neural mechanisms for synthesizing sensory information and producing adaptive behaviors. *Exp. Brain Res.*, **123**, 124–135.

Stein, B.E., London, N., Wilkinson, L.K. & Price, D.D. (1996) Enhancement of perceived visual intensity by auditory stimuli: a psychophysical analysis. *J. Cogn. Neurosci.*, **8**, 497–506.

Stein, B.E. & Meredith, M.A. (1993) *The Merging of the Senses*. MIT Press, Cambridge, MA.

Stepniewska, I. & Kaas, J.H. (1996) Topographic patterns of V2 cortical connections in macaque monkeys. *J. Comp. Neurol.*, **371**, 129–152.

Theoret, H., Merabet, L. & Pascual-Leone, A. (2004) Behavioral and neuroplastic changes in the blind: evidence for functionally relevant cross-modal interactions. *J. Physiol. Paris*, **98**, 221–233.

Ungerleider, L.G. & Desimone, R. (1986) Cortical connections of visual area MT in the macaque. *J. Comp. Neurol.*, **248**, 190–222.

Vanduffel, W., Fize, D., Mandeville, J.B., Nelissen, K., Van Hecke, P., Rosen, B.R., Tootell, R.B. & Orban, G.A. (2001) Visual motion processing investigated using contrast agent-enhanced fMRI in awake behaving monkeys. *Neuron*, **32**, 565–577.

Vezoli, J., Huissoud, C., Falchier, A., Clavagnier, S. & Kennedy, H. (2004) Hierarchical relationships of the frontal eye field. *FENS Forum*, Lisboa, pp. A025.014.

Vroomen, J. & de Gelder, B. (2000) Sound enhances visual perception: cross-modal effects of auditory organization on vision. *J. Exp. Psychol Hum. Percept. Perform.*, **26**, 1583–1590.

Wallace, M.T., Meredith, M.A. & Stein, B.E. (1992) Integration of multiple sensory modalities in cat cortex. *Exp. Brain Res.*, **91**, 484–488.

Wang, Y., Celebrini, S., Jouffrais, C., Trotter, Y. & Barone, P. (2005) Visuo-auditory integration in the monkey: behavioral and neuronal evidences in the primary visual cortex. *6th International Multisensory Research Forum*, Roveroto.

Weeks, R., Horwitz, B., Aziz-Sultan, A., Tian, B., Wessinger, C.M., Cohen, L.G., Hallett, M. & Rauschecker, J.P. (2000) A positron emission tomographic study of auditory localization in the congenitally blind. *J. Neurosci.*, **20**, 2664–2672.

Welch, R.B. & Warren, D.H. (1986) Intersensory interactions. In Boff, K.R., Kaufman, L. & Thomas, J.P. (Eds), *Handbook of Perception and Human Performance*. Wiley, New York, pp. 1–36.

Wong-Riley, M. (1979) Changes in the visual system of monocularly sutured or enucleated cats demonstrable with cytochrome oxidase histochemistry. *Brain Res.*, **171**, 11–28.

Zwiers, M.P., Van Opstal, A.J. & Paige, G.D. (2003) Plasticity in human sound localization induced by compressed spatial vision. *Nat. Neurosci.*, **6**, 175–181.