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Complementary Circuits Connecting the Orbital and Medial Prefrontal Networks with the Temporal, Insular, and Opercular Cortex in the Macaque Monkey

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ABSTRACT

The origin and termination of axonal connections between the orbital and medial prefrontal cortex (OMPFC) and the temporal, insular, and opercular cortex have been analyzed with anterograde and retrograde axonal tracers, injected in the OMPFC or temporal cortex. The results show that there are two distinct, complementary, and reciprocal neural systems, related to the previously defined "orbital" and "medial" prefrontal networks. The orbital prefrontal network, which includes areas in the central and lateral part of the orbital cortex, is connected with vision-related areas in the inferior temporal cortex (especially area TEav) and the fundus and ventral bank of the superior temporal sulcus (STSf/v), and with somatic sensory-related areas in the frontal operculum (OPf) and dysgranular insular area (Id). No connections were found between the orbital network and auditory areas. The orbital network is also connected with taste and olfactory cortical areas and the perirhinal cortex and appears to be involved in assessment of sensory objects, especially food. The medial prefrontal network includes areas on the medial surface of the frontal lobe, medial orbital areas, and two caudolateral orbital areas. It is connected with the rostral superior temporal gyrus (STGr) and the dorsal bank of the superior temporal sulcus (STSd). This region is rostral to the auditory parabelt areas, and there are only relatively light connections between the auditory areas and the medial network. This system, which is also connected with the entorhinal, parahippocampal, and cingulate/retrosplenial cortex, may be involved in emotion and other self-referential processes. J. Comp. Neurol. 506:659–693, 2008. © 2007 Wiley-Liss, Inc.

Indexing terms: OMPFC; orbital network; medial network; superior temporal gyrus; auditory cortex; inferior temporal cortex; superior temporal sulcus; insula; connections

A number of studies over the past 30–40 years have documented substantial and diverse connections between the prefrontal cortex and the temporal cortex (Kuypers et al., 1965; Pandya and Kuypers, 1969; Jones and Powell, 1970; Chavis and Pandya, 1976; Barbas and Mesulam, 1981, 1985; Kawamura and Naito, 1984; Shiwa, 1987; Barbas, 1988, 1993; Seltzer and Pandya, 1989; Ungerleider et al., 1989; Webster et al., 1994; Romanski et al., 1999a; Petrides and Pandya, 2002). Many of these connections are related to the dorsolateral and ventrolateral prefrontal cortex, but there are also substantial connections with the orbital and medial prefrontal cortex (OMPFC). In spite of this extensive literature, however, most of the studies have not clearly related the organiza-

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tion of connections to distinct anatomical circuits or to different functional systems within the OMPFC.

In a previous study from this laboratory, Carmichael and Price (1995b) showed specific projections from the inferior and superior temporal cortex to the orbital prefrontal cortex. The inferior temporal cortex (area TE) projects to specific areas in the lateral orbital cortex, presumably relaying visual sensory information. On the other hand, the rostral superior temporal cortex is connected to restricted regions in the caudolateral part of the orbital cortex. Projections from the temporal cortex to the medial prefrontal cortex and the frontal pole were not reported in that study.

Later studies have shown that these connections are probably related to "orbital" and "medial" prefrontal networks that were defined on the basis of corticocortical connections within the OMPFC (Carmichael and Price, 1996). The "orbital" network includes most of the areas in the central and lateral part of the orbital surface, whereas the "medial" network includes areas on the medial wall plus a restricted region in the caudolateral part of the orbital cortex. Areas within each network are preferen-

Abbreviations

1–2	somatosensory areas 1 and 2
3a/b	somatosensory areas 3a and 3b
4	primary motor cortex
5	somatosensory area 5
6DC	dorsal premotor area 6, caudal subdivision
6DR	dorsal premotor area 6, rostral subdivision
6Va	ventral premotor area
6Vb	ventral premotor area
7a	visual area 7a
7b	somatosensory area 7b
7op	area 7op (parietal operculum)
23a/b/c	posterior cingulate cortex
v23b	area v23b in posterior cingulate cortex
24a/b/c	anterior cingulate cortex
24a′/b′/c′	subregions in the anterior cingulate cortex
29/30	retrosplenial cortex
31	area in the posterior cingulate gyrus
28	entorhinal cortex
35	area 35 of the perirhinal cortex
36c	area 36 of the perirhinal cortex, caudal subregion
36p	area 36 of the perirhinal cortex, temporal-polar subregion
36r	area 36 of the perirhinal cortex, rostral subregion
AB	accessory basal nucleus of amygdala
ac	anterior commissure
AI	auditory area I, core region of the auditory cortex
AL	anterior lateral, belt region of the auditory cortex
amts	anterior middle temporal sulcus
amy	amygdala
asl	arcuate sulcus lower limb
asu	arcuate sulcus upper limb
B	basal nucleus of amygdala
C	caudal
CC	corpus callosum
CA1	CA1 subfield of the hippocampus
cas	calcarine sulcus
cd	caudate nucleus
cis	cingulate sulcus
CL	caudal lateral, belt region of the auditory cortex
cla	claustrum
CM	caudomedial, belt region of the auditory cortex
CPB	caudal parabelt area
cs	central sulcus
F1	agranular frontal area F1
F2	agranular frontal area F2
F3	agranular frontal area F3
F4	agranular frontal area F4
F5	agranular frontal area F5
F6	agranular frontal area F6
F7	agranular frontal area F7
G	gustatory cortex
Iac	caudal agranular insular area
Iai	intermediate agranular insula area
Ial	lateral agranular insula area
Iam	medial agranular insula area
Iapl	posterolateral agranular insula area
Iapm	posteromedial agranular insula area
Id	dysgranular insula
Ig	granular insula
ips	intraparietal sulcus
L	lateral
Ld	lateral nucleus of amygdala, dorsal subdivision
LGN	lateral geniculate nucleus
LIPd	lateral intraparietal area, dorsal subdivision
LIPv	lateral intraparietal area, ventral subdivision
ls	lateral sulcus
lv	lateral ventricle
Lv	lateral nucleus of amygdala, ventral subdivision
M	medial
NA	nucleus accumbens
OMPFC	orbital and medial prefrontal cortex
OPf	frontal opercular area
OT	olfactory tubercle
ots	occipitotemporal sulcus
PFC	prefrontal cortex
PR	rostroventral parietal area
PrCO	precentral opercular area
preSMA	presupplementary motor area
pu	putamen
Pir	piriform cortex
pros	prosubiculum
PV	parietal ventral area
R	rostral
R	rostral, core region of the auditory cortex
RM	rostromedial, belt region of the auditory cortex
RPB	rostral parabelt area
Ri	retroinsula
RT	rostrotemporal, core region of the auditory cortex
RTL	lateral rostrotemporal, belt region of the auditory cortex
RTM	medial rostrotemporal, belt region of the auditory cortex
RTp	rostrotemporal ("p" refers to polar)
rs	rhinal sulcus
sas	spur of the arcuate sulcus
SII	secondary somatosensory area
SMA	supplementary motor area
STGr	superior temporal gyrus, rostral part
sts	superior temporal sulcus
STSd	dorsal bank of STS
STSf	fundus of STS
STSv	ventral bank of STS
TEad	dorsal subregion of anterior TE
TEav	ventral subregion of anterior TE
TEO	area TEO
TEpd	dorsal subregion of posterior TE
TEpv	ventral subregion of posterior TE
TF	area TF of the parahippocampal cortex
TFO	area TFO of the parahippocampal cortex
TG	temporal pole
TGa	agranular part of the temporal pole
TGdd	dysgranular part of the dorsal temporal pole
TGsts	STS part of the temporal pole
TGvd	dysgranular part of the ventral temporal pole
TGvg	granular part of the ventral temporal pole
TH	area TH of the parahippocampal cortex
Tpt	temporoparietal area
V1	visual area 1 (primary visual cortex)
V3v	visual area 3, ventral part
V4	visual area 4
V4v	visual area 4, ventral part
VIP	ventral intraparietal area
vlPFC	ventrolateral prefrontal cortex

TABLE 1. Retrograde and Anterograde Tracer Injections in OMPFC[1]

Case n	Area(s) injected	Tracer	Figure no.
Retrograde tracer injections in the medial network			
1 (OM66)	32, 10m caudal and 14r	FB	3, 4
2 (OM64)	10m rostral	FB	8
3 (OM64)	9	DY	8
4 (OM15)	13a	DY	9
5 (OM15)	lai	FB	9
6 (OM7)	12o	FB	Not shown
Retrograde tracer injections in the orbital network			
7 (OM66)	13m	DY	3, 4
8 (OM67)	11l	FB	10
9 (OM69)	12r and 45/46v	LY	Not shown
Anterograde tracer injections in the medial network			
10 (OM49)	25	BDA	11
11 (OM36)	10m rostral	BDA	12A
12 (OM35)	32/10m caudal	BDA	12B
13 (OM39)	10m caudal/14r	BDA	12C
14 (OM31)	12o	BDA	12D
15 (OM19)	13a	Amino acid (AA)	12E
16 (OM38)	10o	BDA	12F
Anterograde tracer injections in the orbital network			
17 (OM69)	12r and 45/46v	LY	13
18 (OM42)	13l	BDA	14A
19 (OM30)	12m	BDA	14B
20 (OM27)	11l	BDA	14C

[1]See Figure 2. For abbreviations, see list.

TABLE 2. Retrograde and Anterograde Tracer Injections in the Temporal Cortex[1]

Inj. no (case no.)	Area injected	Tracer	Figure no.
1 (OM55)	Rostral STG (STGr) /STS lip	DY (retrograde)	6, 7
2 (OM59)	Rostral STG (STGr)	DY (retrograde)	15A
3 (OM68)	Rostral STG (STGr)	DY (retrograde)	15B, 16B
4 (OM68)	Rostral auditory belt/parabelt	BDA (anterograde)	Not shown
5 (OM68)	Rostral auditory belt/parabelt	FB (retrograde)	15C, 16C
6 (OM62)	Caudal auditory parabelt	DY (retrograde)	15D, 16D
7 (OM59)	TEad/TEav	FB (retrograde)	17A
8 (OM71)	TEav	FB (retrograde)	17B
9 (OM71)	TEav	BDA (anterograde)	Not shown
10 (OM57)	TEpd	FB (retrograde)	17C
11 (OM63)	STS fundus (STSf)	CTb (retrograde)	Not shown
12 (OM59)	STS dorsal bank (STSd)	LY (anterograde)	18
13 (OM59)	STS ventral bank (STSv)	BDA (anterograde)	19
14 (OM55)	STS ventral bank (STSv)	CTb (retrograde)	6, 7

[1]See Figure 5. For abbreviations, see list.

tially interconnected, and the two networks also have differential connections with the temporal cortex and other parts of the brain (Carmichael and Price, 1996; Öngür and Price, 2000; Ferry et al., 2000; Kondo et al., 2003, 2005; Saleem and Price, 2005). For example, the dorsal part of the temporal pole, which is closely related to the rostral superior temporal cortex (gyrus), was found to be connected with the medial network. In contrast, the ventral part of the temporal pole, which is related to the inferior temporal cortex, is connected with the orbital network (Kondo et al., 2003).

In this study, we have further investigated these systems, with injections of anterograde and retrograde axonal tracers into both the OMPFC and subregions of the temporal cortex, including the rostral part of the superior temporal gyrus (STGr), the auditory belt and parabelt areas, the superior temporal sulcus (STS), and subregions of area TE. The experiments have greatly expanded our understanding of the extent and complementary organization of these connections. The medial prefrontal network interacts with the rostral STG and the dorsal bank of the STS (STSd); the connections largely but not completely avoid the auditory belt and parabelt areas in the ventral bank of the lateral sulcus and the caudodorsal STG. The orbital prefrontal network interacts preferentially with areas within the ventral bank and fundus of the STS (STSv/f), and with area TE, most of which are involved in visual processing. In addition, the orbital network is connected with somatic sensory-related areas in the frontal operculum (OPf) and the dysgranular insula (Id).

MATERIALS AND METHODS

Retrograde and anterograde tracers were injected into subregions of the OMPFC and the temporal cortex in adult cynomolgous monkeys (*Macaca fascicularis*; see Tables 1 and 2). In addition, a number of cases with tracer injections in the OMPFC, which had been prepared and used in previous studies (Carmichael and Price, 1995a,b, 1996; Kondo et al., 2005), were reexamined and reanalyzed in relation to the connections with the temporal cortex. All animal protocols were reviewed and approved by the Animal Studies Committee of Washington University, St. Louis, and were in compliance with NIH guidelines for the care and use of laboratory animals.

MRI, surgery, and tracer injection

The tracers were injected during aseptic surgery under general anesthesia. Prior to surgery, each monkey was anesthetized (see below) and placed in an MRI-compatible stereotaxic frame. An MRI scan (T-1 MPRAGE 3D image, with 0.8- or 1.0-mm isometric voxels) was then obtained by using a 1.5-T scanner, using a receive-only or volume coil placed over the top of the head of the animal. Stereotaxic coordinates for each desired injection site in the temporal cortex and OMPFC that were specific for each individual animal were derived without correction from the MR images. These individual-specific coordinates were compared with coordinates from the atlas of Szabo and Cowan (1984). Electrophysiological recording was used to further refine the coordinates for deep injections (see below).

For the surgery (also for MRI), anesthesia was induced by intramuscular injection of ketamine (10 mg/kg) and xylazine (0.67 mg/kg). The animals were then intubated, and surgical anesthesia was initiated with a gaseous mixture of oxygen, nitrous oxide, and halothane or isofluorane. Once anesthesia was established, the animals were placed in a stereotaxic apparatus, and the scalp was incised. Craniotomies were made in the skull at the sites indicated by the stereotaxic analysis. The midline was defined from the midsagittal sinus. After surgery, a long-lasting analgesic, buprenorphine (0.1 mg/kg, i.m.), was given as the animal was brought out of anesthesia.

Prior to tracer injections into the deep cortical areas of OMPFC and the temporal cortex, a tungsten electrode was inserted along the expected injection track for electrophysiological recording of spontaneous, multiunit activity. This allowed the determination of the vertical coordinates of structural landmarks such as the boundaries between gray and white matter, the position of sulci, and the bottom of the brain, which were used to correct the vertical coordinates determined from the MRI scans. For most of the temporal cortex (STG, STS, and TE) injections, the superior temporal sulcus and lateral sulcus were exposed after craniotomy, and the injection sites were determined with reference to these sulci and the stereotaxic coordi-

nates derived from MRI. These temporal cortex injections did not require electrophysiological recordings.

Aqueous solutions of three retrograde tracers (Fast Blue [FB; Sigma, St. Louis, MO; Dr. Illing; 2%], Diamidino Yellow [DY; Sigma; 4%], and cholera toxin subunit B [CTb; List Biological, Campbell, OR; 1–2%]), an anterograde tracer (biotinylated dextran amine [BDA; Molecular Probes, Eugene, OR; 10%]), two bidirectional tracers (Fluoro Ruby [FR; Molecular Probes, 5% or 10%], and Lucifer Yellow [LY; Molecular Probes, 5% or 10%]) were injected in each animal. The injections were made through micropipettes with an air pressure system that applied 25-msec air pulses to the pipette. The air pressure was adjusted so that very small volumes of tracer solution were injected with each pulse. The volume of injection was calculated by monitoring the meniscus level of the micropipette (1-mm movement delivered 0.05 or 0.13 μl, calculated from the internal diameter of the shaft of the pipette). The volume of tracers injected varied between 0.1 and 1.2 μl, depending on the sensitivity of tracers. To avoid spread of tracer into areas along the pipette track, the micropipette was left in place for 30 minutes after the injection was finished. With this procedure, there was little spread of tracer into the overlying cortex or white matter.

Perfusion and histological processing

After a survival period of 2 weeks, the animals were anesthetized with ketamine (10 mg/kg, i.m.), followed by sodium pentobarbital (25–30 mg/kg i.v.), and perfused with a pH shift fixation method as described by Carmichael and Price (1994), with slight modifications. In this method, the animals were first perfused transcardially with warm heparinized saline, followed by a sequence of cold 4% paraformaldehyde in 0.1 M sodium acetate buffer (pH 6.5), then 4% paraformaldehyde in 0.1 M borate buffer (pH 9.5), and finally 4% paraformaldehyde and 10% sucrose in borate buffer. The brain was blocked stereotaxically, then removed, photographed, and postfixed for 6 hours in the final fixative/sucrose solution, and then transferred through 20 and 30% sucrose in 0.1 M phosphate buffer (pH 7.2–7.4) at 4°C.

After 3–4 days, the brain blocks were frozen in dry ice and isopentane and cut coronally at 50-μm thickness on a sliding microtome. An alternating series of sections was processed for each tracer, usually 500-μm intervals between adjacent sections in each series. The fluorescent tracers FB and DY were analyzed from unstained sections. BDA was processed directly with the avidin-biotin-peroxidase method. The other tracers (CTb, FR, and LY) were processed immunohistochemically with an avidin-biotin-horseradish peroxidase method (Carmichael et al., 1994; Haber et al., 2000). For these tracers, the sections were first processed to block the biotin from the injected BDA (Avidin/Biotin blocking kit, Vector, Burlingame, CA) and then incubated for 3–3.5 days in the primary antibody (anti-CTb, List Biological #703; 1:10,000–20,000; anti-tetramethylrhodamine [for FR] and anti-Lucifer Yellow, Molecular Probes #A-6397 and #A-5750; 1:1,000). The sections were then processed with the appropriate biotinylated secondary antibody and avidin/biotin staining kit (Vector) with diaminobenzidene as the chromogen. For BDA, LY, and FR, the immunostaining was enhanced with a silver/gold intensification method, which made the labeled axons and cells visible with darkfield illumination (Carmichael and Price, 1994). Additional series of sections were processed with the Nissl, acetylcholinesterase (AChE) and myelin (Gallyas) stains, or immunohistochemically with antibodies against parvalbumin (Sigma, #P3171 and #P3088) and a nonphosphorylated epitope of the neurofilament protein (recognized by the SMI-32 antibody; Sternberger Monoclonals, Baltimore, MD).

The parvalbumin antibody was raised against parvalbumin from carp muscle. It was determined to be specific by immunoblotting (Western blot) and to specifically stain the 12,000 molecular weight band that was identified as parvalbumin by Ca-binding (Sigma data sheet). The SMI-32 antibody recognizes a nonphosphorylated epitope on neurofilament H. It was shown to be specific by immunoblot, where it recognizes a double band at MW 200,000 and 180,000, which merge into a single neurofilament H line on two-dimensional blots (Sternberger and Sternberger, 1983; Goldstein et al., 1987). The antibody has been shown to stain a subpopulation of pyramidal cells in the neocortex (e.g., Campbell and Morrison, 1989; Hof and Morrison, 1995); the pattern of staining seen in this study corresponds to well-established patterns from many previous studies.

Data analysis and presentation of illustrations

The location and the extent of each injection site and the spatial distribution of labeled cell bodies and axonal varicosities were plotted from the histological sections with a microscope digitizer system that has encoders attached to the microscope stage and is interfaced with a personal computer (AccuStage, Shoreview, MN). Cortical boundaries and other landmarks were added to these plots by camera lucida drawings of adjacent Nissl-, parvalbumin-, AChE-, and myelin-stained sections. With the retrograde tracers, each labeled cell was plotted as a single point. With the anterograde tracers, varicosities along the labeled axons were plotted. Due to the very large number of varicosities in each projection, they were plotted in rows, with every other row skipped; this meant that approximately half the varicosities were plotted. Because the varicosities largely correspond to synaptic boutons, the varicosity maps represent the synaptic distribution of the labeled projection.

The files prepared with the microscope digitizer were transferred to the computer-aided design program Canvas 8.0 (Deneba, Miami, FL), in order to add the section outlines, boundaries between gray and white matter and between architectonic areas, and labels. The distribution of the labeled cells or axonal varicosities was not altered, and they retained their exact position as plotted at the microscope. The maps of individual sections were then combined to make the figures.

Unfolded maps of the prefrontal and temporal cortical regions were prepared in a similar manner as described previously (Carmichael and Price, 1994; Kondo et al., 2003). Briefly, lines were drawn through layer IV, or the boundary between layers III and V, in serial coronal sections, usually sampled at 0.5–1-mm intervals. For the prefrontal cortex, these lines were "cut" at the depth of the principal sulcus and then "pulled out" to straight lines and aligned to construct unfolded maps (for example, see Fig. 7C,D, "Scissors mark"). For the temporal cortical regions, the dorsal edge of the unfolded maps was at the dorsal lip of the lateral sulcus, whereas the ventral edge was at the

medial lip of the anterior middle temporal sulcus (corresponding to area TEav). Thus in each unfolded map of the temporal cortex, the following regions are included: the somatic sensory-related cortex, insula, auditory cortex, superior temporal gyrus, banks of the superior temporal sulcus, temporal pole, and different subregions of area TE (for example, see Fig. 8A). The distribution of labeling was then transformed onto unfolded maps from the plots of coronal sections made with the microscope digitizer system. The number of labeled cells in a column across the thickness of the cortex that was 0.83 mm wide at layer IV was counted from the digitized map and transferred onto the unfolded maps as circles of four different sizes. The largest circle represents more than 17 cells in a column 0.83 mm wide through all layers, the second largest circle between 8 and 16 cells, the third largest between 3 and 7 cells, and the smallest circle indicates either one or two cells (for example, see Fig. 7).

Photomicrographs to document the tracer injection sites and patterns of labeling were taken with a Nikon DXM1200 CCD camera attached to the microscope, using Nikon ACT-1 image acquisition software. The images were transferred into Adobe (San Jose, CA) Photoshop for adjustment of brightness and contrast to show the labeled axons optimally and to size the images for inclusion into a plate.

Terminology

In the prefrontal cortex, the architectonic subdivision of the OMPFC by Carmichael and Price (1994) will be used (Fig. 1A,B). Twenty-two areas were recognized, based on staining with multiple methods and on connections. These areas were divided into medial and orbital prefrontal networks, based on corticocortical connections within the OMPFC (Carmichael and Price, 1996). The "medial prefrontal network" consists of areas on the medial wall (areas 10m, 10o, 24, 25, and 32) and the gyrus rectus (areas 11m, 14c, and 14r), plus area Iai in the caudolateral orbital cortex. In this study, rostral and caudal parts of area 10m have been recognized (areas 10mr and 10mc) based on evidence from this and previous reports that these regions have relatively different connections. The "orbital prefrontal network" consists of areas in the central and lateral part of the orbital cortex (areas 11l, 12r, 12l, 12m, 13l, and 13m) as well as several agranular insular areas in the caudal orbital cortex (areas Iam, Iapm, Ial, and Iapl). Two areas on the gyrus rectus (areas 13a and 13b) and one area in the caudolateral orbital cortex (area 12o) have connections with both networks and have been considered intermediate (see Discussion).

As described in previous studies, the inferior temporal area TE will be subdivided into four subdivisions, TEad, TEav, TEpd, and TEpv (Fig. 1C,D; Yukie et al., 1990; Saleem and Tanaka, 1996; Saleem et al., 2000; Saleem et al., 2007; see also Saleem and Logothetis 2007). The architectonic analysis by Saleem et al. (2007) will be used for the perirhinal and parahippocampal areas. The subdivision of the auditory cortex into core areas (AI, R, and RT), lateral (RTL, AL, ML, and CL) and medial (RTM, RM, MM, and CM) belt areas, and parabelt areas (RPB and CPB) is based on the descriptions by Kaas and his colleagues (Fig. 1E; Hackett et al. 1998; Kaas and Hackett, 2000). The only difference is that a rostral continuation of the core and belt is recognized as area RTp, based on dense parvalbumin staining, which continues rostrally into the dorsomedial aspect of the temporal pole (Saleem et al., 2007). Hackett et al. (1999) also recognized a rostral superior temporal gyrus area (STGr) rostrolateral to the auditory areas (Fig. 1E). This area largely corresponds to areas TS1 and TS2 of Galaburda and Pandya (1983). Finally, areas within the rostral part of the superior temporal sulcus are referred to as STSd, STSf, and STSv, for the dorsal bank, fundus, and ventral bank of the sulcus, respectively (Saleem et al., 2000). For a description of other cortical areas illustrated in this study, see Saleem and Logothetis (2007).

The insula and frontoparietal operculum contain several areas relevant to this study (Fig. 1F). The insula is divided into three major regions, based on the presence and density of granular layer IV (Mesulam and Mufson, 1982). The agranular region occupies the rostroventral part of the insula and has been divided into several areas. In addition to the areas on the posterior orbital surface and the anterior insula that were recognized by Carmichael and Price (1994), a caudal agranular insular area (Iac) extends caudally through the rostral two-thirds of the insula in the fundus of the inferior limiting sulcus. The dysgranular insular area (Id) occupies the central part of the insula, dorsal to Iac. The dorsal and caudal part of the insula is occupied by the granular insular area (Ig), beginning rostrally in the superior limiting sulcus and extending back into the caudal part of the insula.

Several areas related to somatic sensation occupy the dorsal bank of the lateral sulcus and frontoparietal operculum (Fig. 1F). Most of this region has been referred to as the second somatic sensory area (SII), based on architectonic and connectional criteria (Jones and Burton, 1976; Cipolloni and Pandya, 1999; Saleem and Logothetis, 2007). Detailed anatomical and electrophysiological data, however, have indicated that the region can be divided into several areas, with SII proper restricted to the caudal part of the parietal operculum (Robinson and Burton, 1980; Burton et al., 1995). Rostral to SII is another area with a physiologically defined somatotopic map, which has been referred to as the parietal ventral area (PV; Krubitzer et al., 1995). Areas SII and PV appear to correspond to the opercular areas 1 and 4 (OP1 and OP4) that have been defined in humans (Eickhoff et al., 2006; Burton et al., 2008). Rostral to area PV, the operculum is occupied by a poorly defined area that has been termed the rostroventral parietal area (PR; Disbrow et al., 2003). Because area PR has not been defined architectonically and its boundaries are uncertain, we will refer to the cortex rostral to area PV as the frontal operculum (area OPf). Although there is some evidence, based on connections and differences in staining for parvalbumin and with the antibody SMI-32, that area OPf may be divisible into rostral and caudal subdivisions, this will not be done here.

RESULTS

Complementary projections between the orbital and medial prefrontal networks and the temporal cortex

Experiments based on 34 tracer injections (Tables 1, 2) demonstrate that there are two distinct and largely complementary circuits that relate the two networks within the OMPFC to the temporal, insular, and opercular cortex. That is, injections of axonal tracers into either the

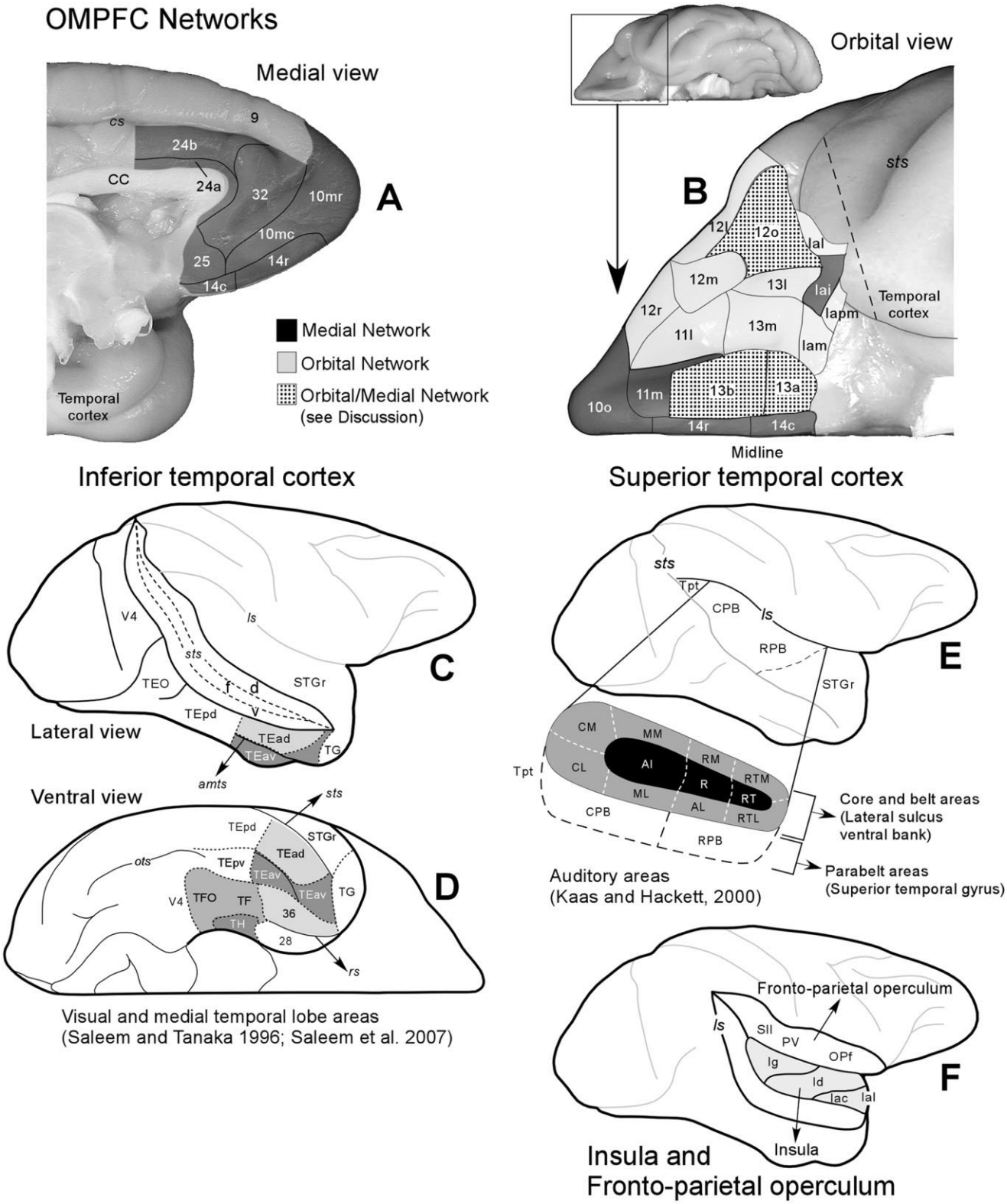


Fig. 1. **A,B:** Architectonic subdivisions of the orbital and medial prefrontal networks in the OMPFC. The medial prefrontal network areas are shown by dark gray shading, and the areas of the orbital prefrontal network are unshaded. The hatched areas are connected with both networks (intermediate areas). An imaginary cut line is made on the temporal pole (dashed line in B) to expose the areas on the caudal orbital surface (Ial, Iai, and Iapm). C–F: Architectonic subdivisions of the superior and inferior temporal cortex and subregions within the lateral sulcus. **C:** The superior temporal sulcus (STS) is opened to show the dorsal bank (d), fundus (f), and ventral bank (v). **D:** The subdivisions of the inferior temporal cortex. **E:** The ventral bank of the lateral sulcus is opened to show the auditory core and belt areas, as defined by Kaas and Hackett (2000). **F:** The lateral sulcus is opened to show the areas in the insular cortex (Ial, Iac, Id, and Ig) and frontoparietal operculum (SII, PV, and OPf). For abbreviations, see list.

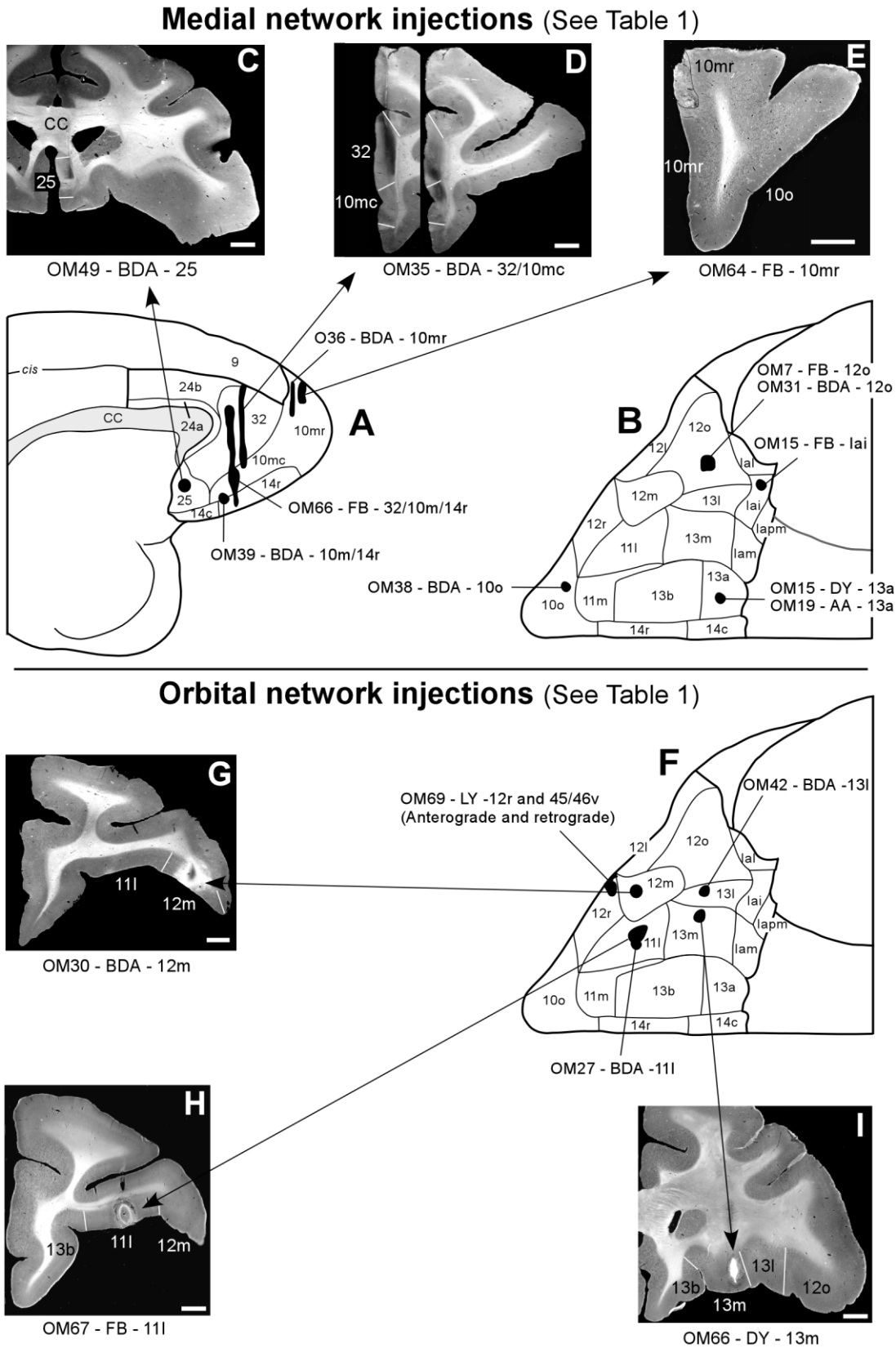


Fig. 2. Location of anterograde and retrograde tracer injection sites in the medial (**A–E**) and orbital (**F–I**) network areas, shown on medial and orbital views of the brain. Examples of the injection sites are also shown in darkfield photomicrographs. See also Table 1. For abbreviations, see list. Scale bar = 2 mm in C–E, G–I (darkfield photomicrographs).

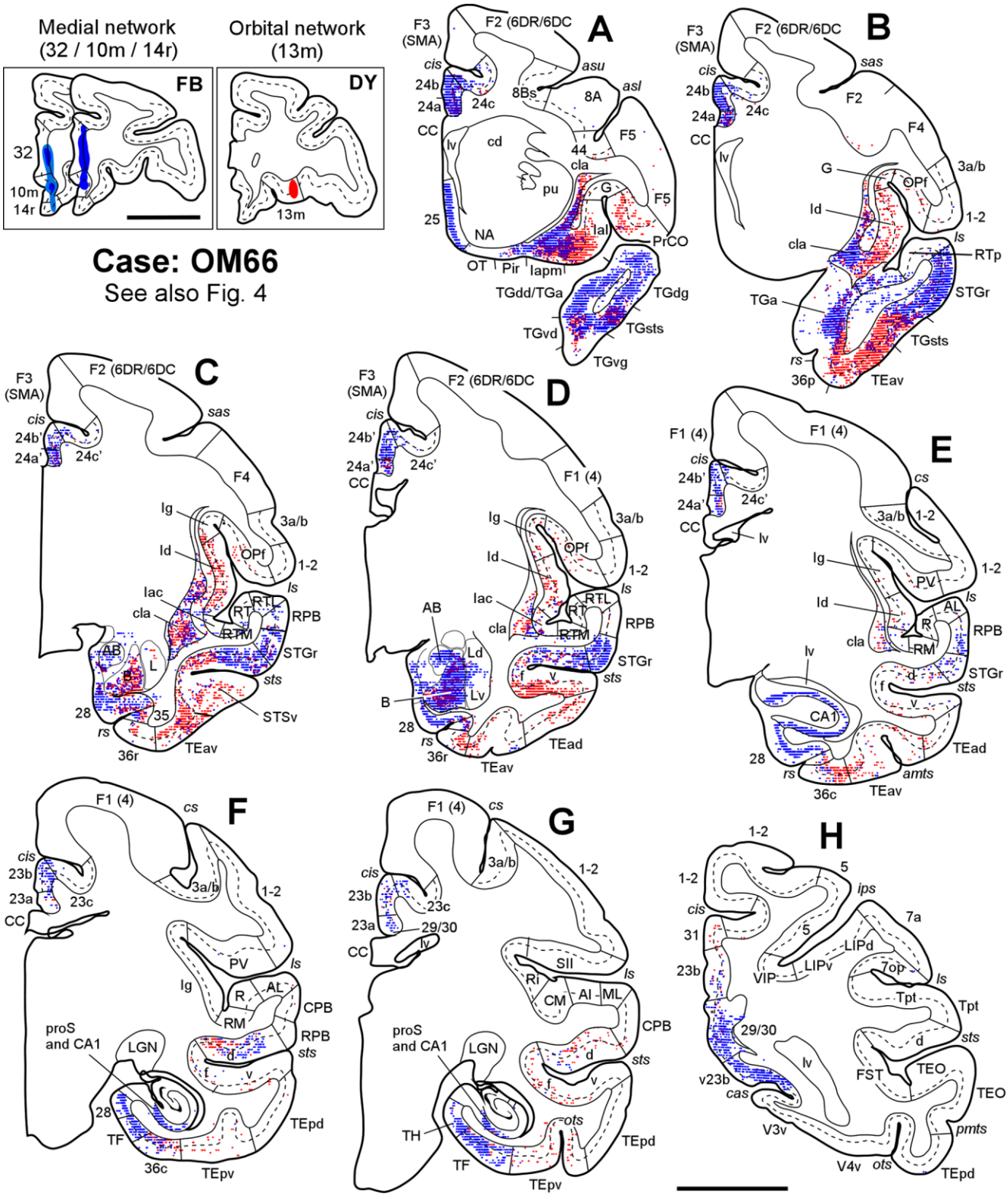


Fig. 3. **A–H:** Distribution of cells in the temporal cortex and other areas that were retrogradely labeled from an injection of FB into the medial network (areas 32/10m/14r) or of DY into the orbital network (area 13m). Each dot represents one retrogradely labeled cell. The dashed lines in the sections indicate layer IV. Note that cells projecting to the medial network (blue dots) are located in the dorsal temporal pole, rostral superior temporal gyrus (STGr), dorsal bank of the superior temporal sulcus (STSd), and entorhinal, parahippocampal, cingulate and retrosplenial cortex. In contrast, cells projecting to the orbital network (red dots) are found in area TE, the ventral bank and fundus of the STS (STSv/f), the dysgranular insula (Id), the frontal opercular area (OPf), and the perirhinal cortex. See also Figure 4. For abbreviations, see list. Scale bar = 10 mm in top panel and H (applies to A–H).

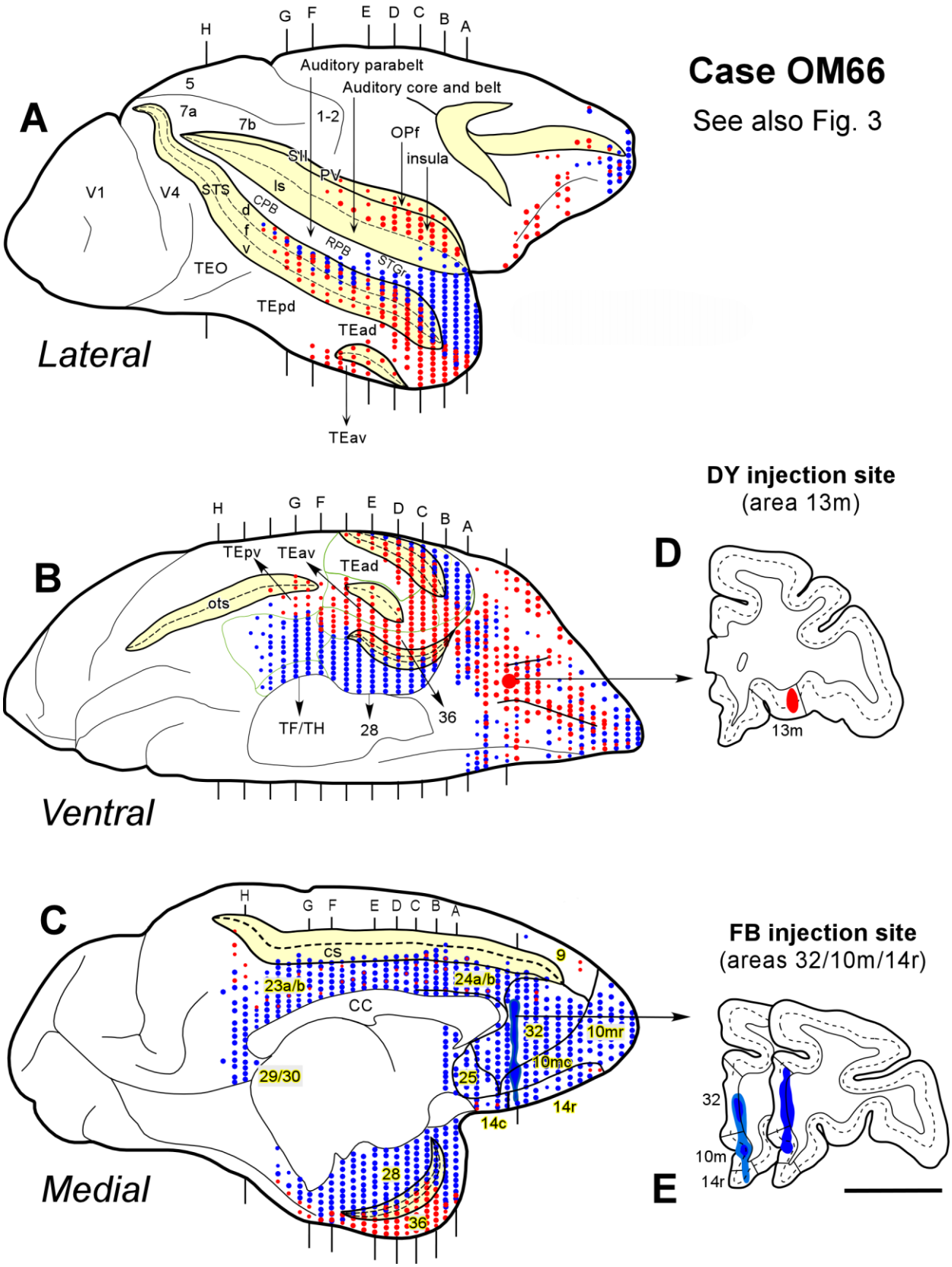


Fig. 4. **A–C:** Lateral (A), ventral (B), and medial (C) brain surface maps showing the distribution of cells in the temporal, insular, opercular, and frontal cortex that were retrogradely labeled from injections of FB into the medial network (areas 32/10m/14r, blue) or DY into the orbital network (area 13m, red). **D,E:** The corresponding injection sites in the frontal cortex. These surface maps were created based on the data shown in Figure 3. For abbreviations, see list. Scale bar = 10 mm in E (applies to D–E).

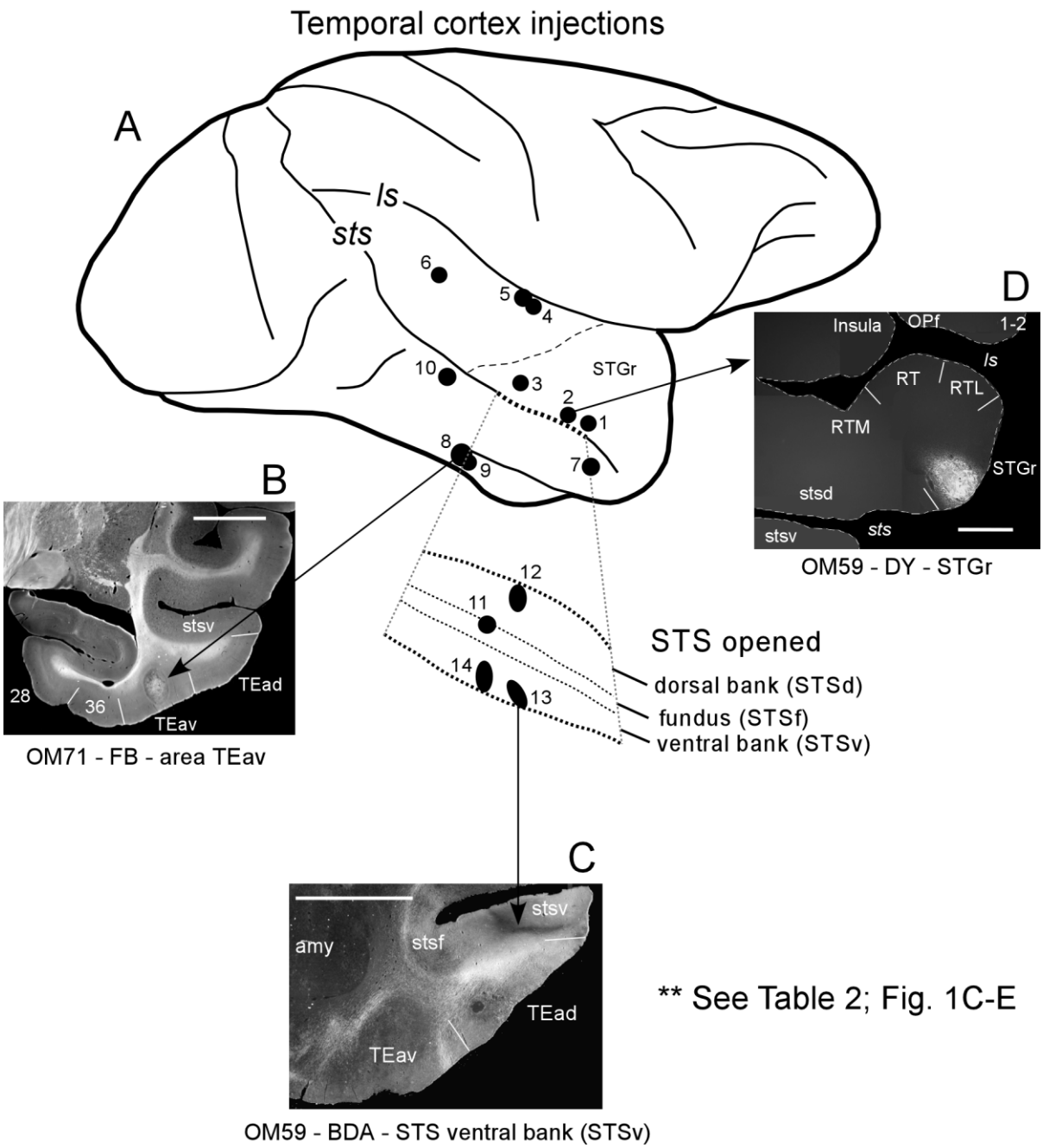


Fig. 5. **A:** Locations of the anterograde and retrograde tracer injection sites (# 1–14) in the superior and inferior temporal cortex and the superior temporal sulcus (see also Table 2). **B–D:** Examples of the injection sites are also illustrated in darkfield photomicrographs. For abbreviations, see list. Scale bar = 5 mm in B,C; 1 mm in D.

orbital or the medial prefrontal network label different patterns of transported label within the inferior or superior temporal cortex, respectively. Similarly, injections into these restricted parts of the temporal cortex label complementary patterns of transported label in either the orbital or medial networks. Initially, experiments that illustrate the overall pattern of these complementary systems will be described, based on retrograde tracer injections in both the OMPFC and the temporal cortex. Subsequently, other experiments will be used to demonstrate that there is a degree of organization within both systems.

Retrograde tracer injections in the OMPFC. In case OM66, two injections of retrograde axonal tracers were made into the medial prefrontal cortex and the central orbital cortex (Fig. 2A,F,I). A large injection of FB involved three areas in the medial prefrontal cortex (Fig. 2A; areas 32, caudal 10m, and 14r), which encompass a large part of the medial prefrontal network. A smaller injection

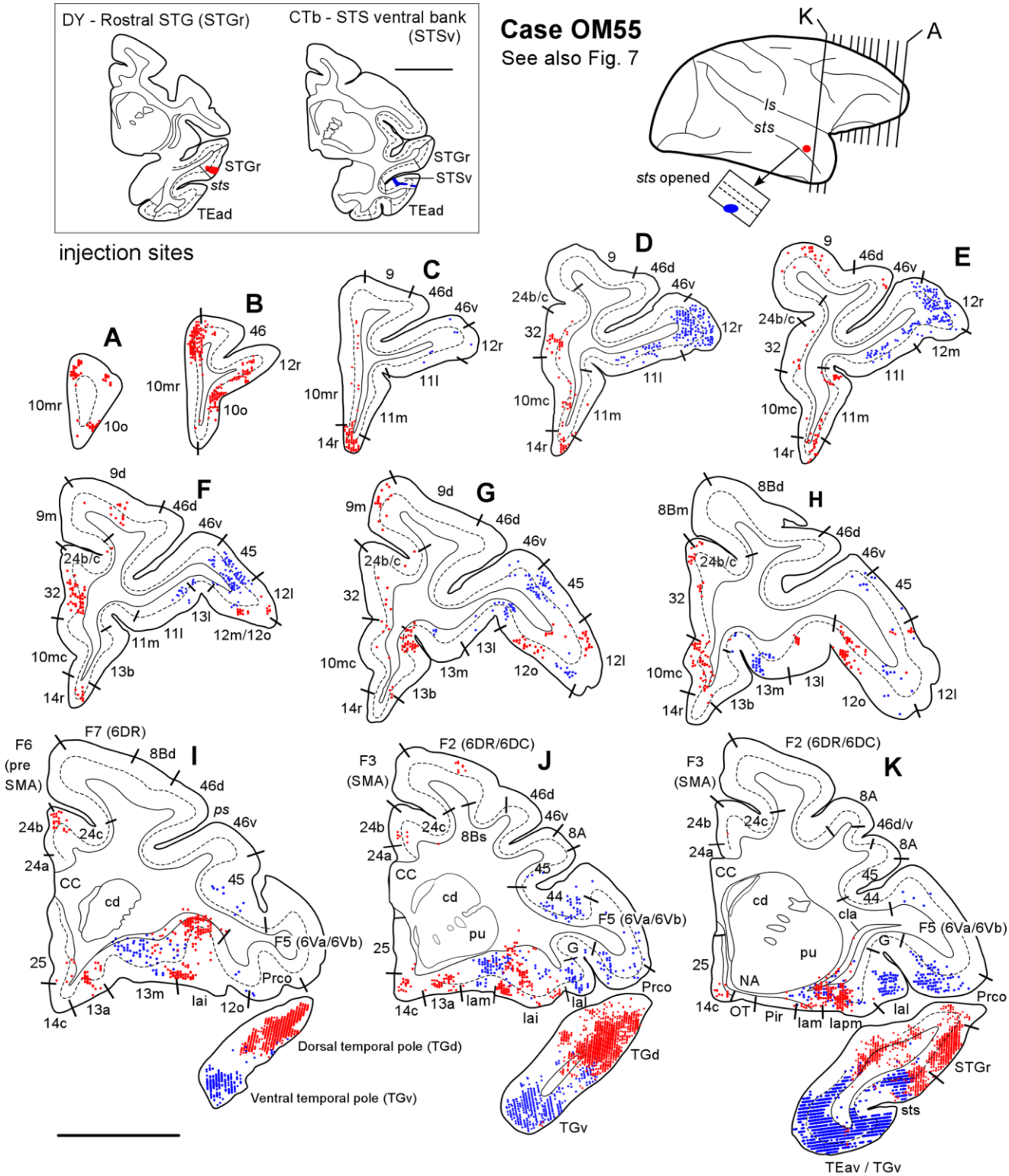


Fig. 6. **A–K:** Distribution of cells in the prefrontal cortex and the temporal pole that were retrogradely labeled from an injection of DY into the rostral superior temporal gyrus (STGr) or of CTb into the ventral bank and ventral lip of the superior temporal sulcus (STSv). Each dot represents one retrogradely labeled cell. The lines on the lateral view of the brain at the top illustrate the levels of the coronal sections A–K. Dashed lines indicate layer IV or boundary between layers III and V. Note that cells projecting to the STGr (red dots) are located in the medial network areas, including 10mr/c, 13a, 14c/14r, 32, Iai, and the medial part of 12o. In contrast, cells projecting to the STSv (blue dots) are found in the orbital network areas, including 11l, 12r, 12m, 13m/l, Iam, Ial, and also area 45. **I,J:** Also note the complementary distribution of cells in the dorsal and ventral parts of the temporal pole. For abbreviations, see list. Scale bar = 10 mm in top panel and I (applies to A–K).

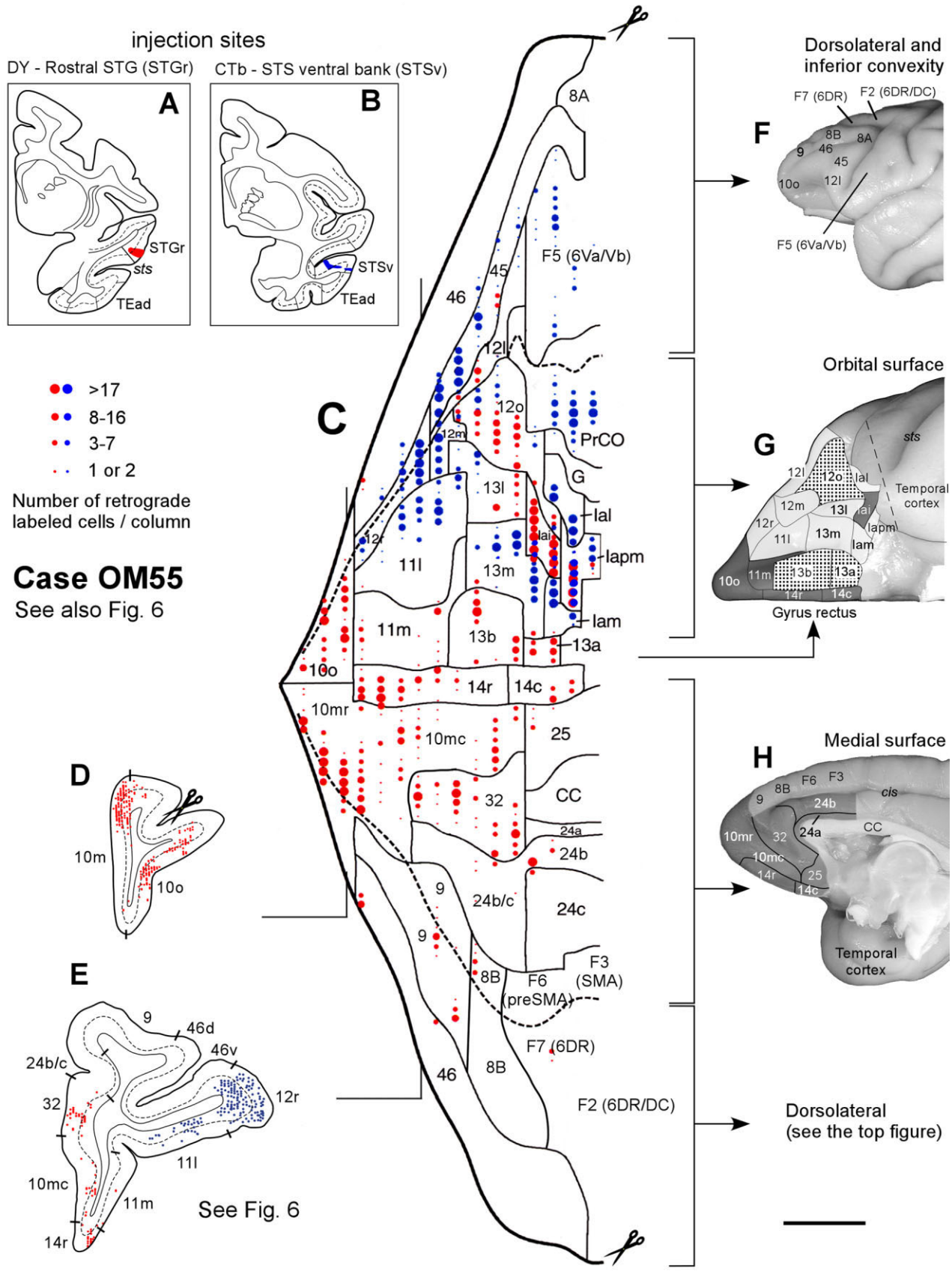

injection sites
DY - Rostral STG (STGr)
CTb - STS ventral bank (STSv)
A
STGr
sts
TEad
B
STSv
TEad
>17
8-16
3-7
1 or 2
Number of retrograde labeled cells / column
Case OM55
See also Fig. 6
C
8A
F5 (6Va/Vb)
46
45
12l
12o
12m
PrCO
G
13l
lal
lapm
lam
13a
12r
11l
13m
11m
13b
10o
14r
14c
10mr
10mc
25
CC
32
24a
24b
9
24b/c
24c
F3 (SMA)
8B
F6 (preSMA)
F7 (6DR)
F2 (6DR/DC)
D
10m
10o
E
9
46d
46v
24b/c
32
12r
11l
10mc
11m
14r
See Fig. 6
Dorsolateral and inferior convexity
F
F7 (6DR)
F2 (6DR/DC)
8B
8A
9
46
45
10o
12l
F5 (6Va/Vb)
Orbital surface
G
sts
12l
12o
lal
Temporal cortex
12m
13l
lapm
12r
11l
13m
lam
10o
11m
13b
13a
14r
14c
Gyrus rectus
Medial surface
H
F6
F3
8B
9
cis
24b
10mr
32
24a
CC
10mc
14r
25
14c
Temporal cortex
Dorsolateral (see the top figure)

Figure 7

of DY was located at the lateral part of area 13m in the center of the orbital prefrontal network (Fig. 2F,I).

Neurons retrogradely labeled from the FB injection in the medial prefrontal cortex were distributed in the dorsal and medial temporal pole (areas TGdg, TGdd, and TGa), STGr, and STSd (Fig. 3A–D, blue dots). Very few if any labeled neurons were found in the caudal STSd, or in the core, belt, or parabelt areas of the auditory cortex (Figs. 3D–H, 4A). Elsewhere in the cerebral cortex, there were labeled cells in the caudal agranular insula area along the ventral circular sulcus (area Iac), rostral and caudal cingulate cortex (areas 24 and 23), retrosplenial cortex (areas 29 and 30), parahippocampal cortex (areas TF and TH), entorhinal cortex (area 28), and hippocampal formation, mainly along the border between the subiculum and CA1 (Figs. 3, 4).

In contrast, cells labeled with DY were found in the ventral temporal pole (areas TGvg, TGvd, and TGsts), areas TEad and TEav, and STSv/f (Fig. 3A–E, red dots). Elsewhere, there were labeled cells in the perirhinal cortex (areas 35 and 36), the dysgranular insula (Id). A few cells were also found in areas OPf, TEpv, the medial part of the STSd, and the cingulate cortex (Figs. 3C–H, 4A). No labeling was found in areas TEpd or TEO.

Very few cells labeled with FB from the medial prefrontal cortex were found in the STSv or in any part of area TE. Similarly, very few cells labeled with DY from the central orbital cortex were found in the STGr. The only area of substantial overlap was in the STSd, and even here, most of the FB cells were in the lateral part of the sulcus, near the lip, whereas most of the DY cells were in the medial part, near the fundus of the sulcus.

Retrograde tracer injections in the temporal cortex. A parallel case to OM66 is provided by OM55, in which retrograde tracer injections were made into the superior and inferior temporal cortex (Figs. 5 [injections 1 and 14], 6). An injection of DY was located in the ventral part of the STGr. A second injection of CTb involved the STSv. Within the temporal cortex, cells labeled with DY were restricted to the STGr and STSd, whereas those labeled with CTb were found in area TE and the STSv/f. There was remarkably little overlap in the STSd between cells labeled with the two tracers, except for a small area near the fundus, at about the level of junction between the amygdala and hippocampus.

In the OMPFC, retrogradely labeled neurons were distributed in patches over relatively large regions, but there was very little overlap between cells labeled with the two tracers (Figs. 6, 7). If the overall patterns are considered, it is apparent that DY labeled cells are restricted to the medial prefrontal network, whereas those labeled with CTb are located in the orbital prefrontal network.

Thus, patches of cells labeled from the injection in the STGr were found in the rostral and caudal parts of area 10m (10mr and 10mc), areas 10o, 11m, 14r, 14c, 32, and Iai, all of which are within the medial network (Figs. 6, 7, red dots). In addition, there were cells in areas 13a, 13b, 12o, and Iapm. Of these, areas 12o and 13a have been associated with both networks. Areas 13b and Iapm were originally considered in the orbital network, but our recent studies have shown that they have many associations with the medial network as well, and with temporal cortical areas connected with the medial network (Carmichael and Price, 1996; Kondo et al., 2005).

In contrast to this pattern, the injection in STSv labeled substantial numbers of cells in areas 11l, 12r, 12o, 13l, 13m, Iam, Iapm, and Ial (Figs 6, 7, blue dots). These areas comprise most of the orbital network. There are also labeled cells in areas 45 and PrCO in the ventrolateral PFC (Fig. 6F–K).

Note that within area 12o the labeled cells were restricted to a subportion of the area. Thus, cells labeled from the STGr were found at the medial edge of 12o (Fig. 6, sections G,H; red dots). In contrast, the cells labeled from the STSv were found at the lateral edge of area 12o, primarily along the junction between 12o and 12l (Fig. 6, sections G, H; blue dots). This suggests that different parts of area 12o may be related to each network, in keeping with previous suggestions that this area is heterogeneous (Carmichael and Price, 1996; An et al., 1998).

The only region of substantial overlap between the labeled cells from the two injections was in areas Iam and Iapm (Figs. 6K, 7). The interpretation of the label in these areas is complicated by the additional presence of label in the claustrum immediately deep to the cortex. In this region the white matter lamina between the cortex and claustrum is very thin, and some claustral cells even overlap the deep layers of the cortex.

These two experiments (OM66 and OM55), with two retrograde axonal tracer injections each, define the two systems of connections between the OMPFC and the temporal cortex. By themselves, however, they do not establish the full extent of the connections or demonstrate whether there is any organization within the two systems. Other experiments, with injections of retrograde and anterograde tracers into restricted areas of the OMPFC or the temporal cortex, will be used to define these points.

Experiments with retrograde tracer injections in the OMPFC

Injections in the medial network. In case OM64, injections of FB and DY were made into area 10mr and area 9, respectively, at the rostrodorsal edge of the medial network (Figs. 2E, 8). Both injections labeled cells in the

Fig. 7. **A–C:** Unfolded map illustrating the distribution of retrogradely labeled cells in the OMPFC following injections of DY into the STGr and CTb into the STSv. This map was created based on the data shown in Figure 6. The circles represent the number of cells in a column 0.83 mm wide across all layers of the cortex. The largest circles represent more than 17 cells/column, the second largest circles between 8 and 16 cells, the third largest circles between 3 and 7 cells, and the smallest circles 1 or 2 cells. The dashed lines on the map represent the ventrolateral and dorsomedial convexities of the frontal lobe. **D,E:** Two of the coronal sections with labeled cells that were used to construct the unfolded map. The scissors marks in C and D indicate that lines were "cut" at the depth of the principal sulcus and then "pulled out" to straight lines and aligned to construct unfolded maps (see Materials and Methods). **F–H:** The corresponding positions of the prefrontal cortex in the map are also indicated in lateral, orbital, and medial views of the brain. Note the complementary distribution of labeled cells following the injection in the STGr (A, red cells) compared with that following the injections in the STSv (B, blue cells). For other details, see Figure 6. For abbreviations, see list. Scale bar = 5 mm applies to "C" only.

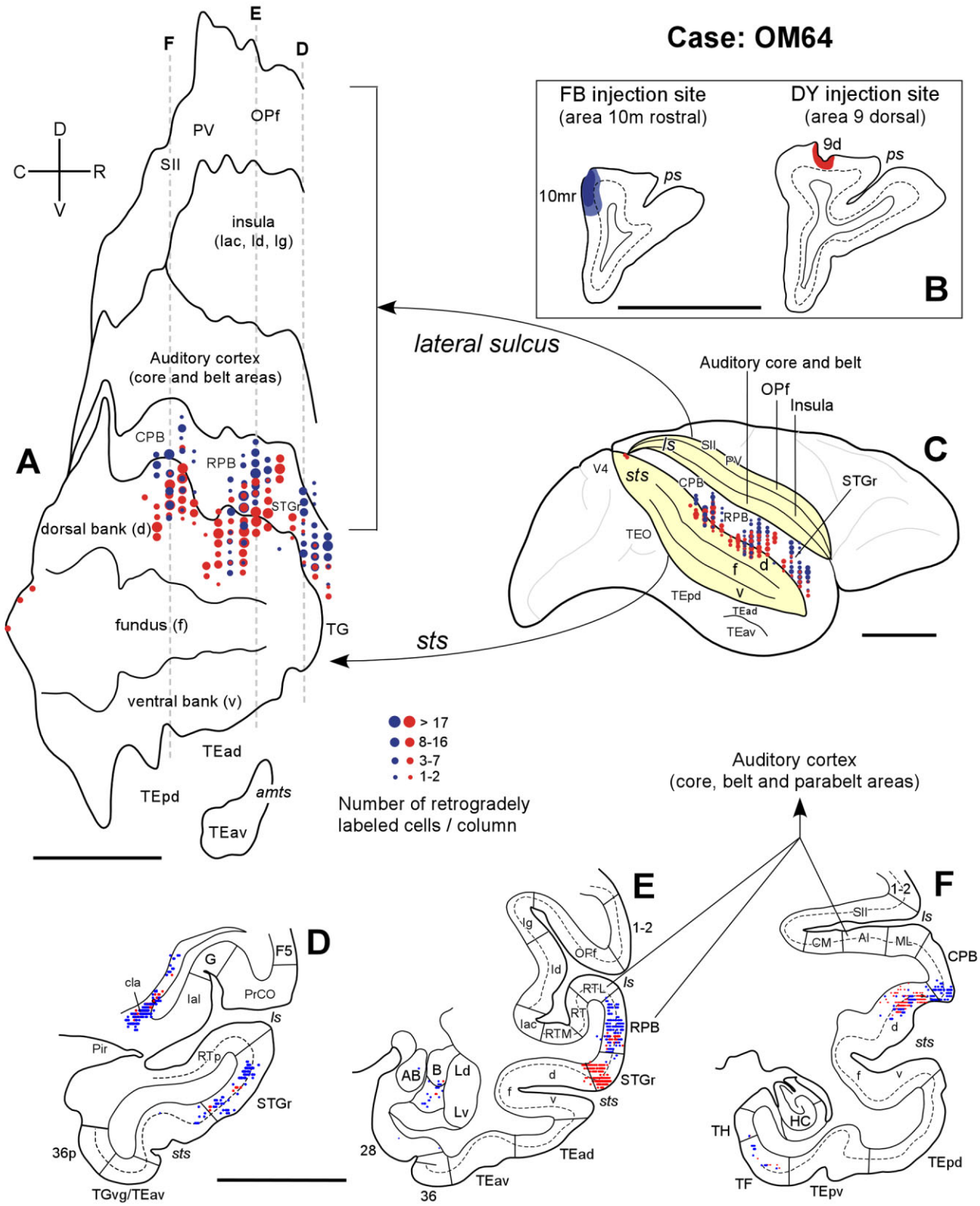


Fig. 8. **A–C:** Unfolded map and lateral view of the brain showing the distribution of retrogradely labeled cells in the superior temporal cortex following injections of FB into rostral area 10m (10mr) and DY into area 9. **D–F:** Three dashed lines in A indicate the levels of three representative coronal sections with labeling. The details about the sizes of the circles are the same as in Figure 7. Note that both injections labeled a patchy distribution of cells in the STGr, the STSd, and to some extent the rostral parabelt area (RPB) of the auditory cortex. Labeling does not extend into the auditory core and belt areas. For abbreviations, see list. Scale bar = 10 mm in A–D (that in D applies to D–F).

STGr and STSd, as were seen with the FB injection in OM66 (Fig. 4). In particular, most of the cells were situated just lateral and rostral to the auditory core and belt areas, and did not extend into them. However, some of the labeled cells extended further caudally in the STG and STSd than was seen in OM66 and may overlap with the parabelt areas (RPB and CPB). In addition, with the smaller injections in OM64, it is apparent that the labeled cells were distributed in patches, which to a large extent interdigitated with each other (Fig. 8). Thus, even though the FB and DY injection sites were very close to each other, they appeared to be related to different populations of neurons within the STGr and STSd.

In case OM15, two small injections of retrograde tracers (DY and FB) were made in restricted region in the caudal part of the OMPFC, in areas 13a and Iai, respectively (Fig. 9). Although these two areas are in the orbital cortex, they have specific connections with other medial network areas and are considered part of the medial network (Carmichael and Price, 1996). From both injections there were retrogradely labeled cells in the STGr and STSd. By comparison with OM64 (Fig. 8), the distribution of the labeled cells was shifted rostrally into the temporal pole and did not extend as far caudally. This was especially true for the cells labeled from area Iai, which were concentrated in the temporal pole. As in OM64, the labeled cells from the two injections were concentrated in patches, which largely interdigitated with each other and had relatively little overlap. There were also labeled cells at the ventral edge of the insula, in area Iac.

Case OM15 also showed some labeled cells in area TEav, which were not labeled from other injections in the medial network (Fig. 9). It is possible that these cells were labeled from slight spread of the tracer into areas of the orbital network that are immediately adjacent to 13a or Iai.

An injection of FB was made into the medial part of area 12o in OM7 (Fig. 2B). Although area 12o has connections with both medial and orbital networks, the medial part of this area is predominantly related to the medial network. In this case the labeled cells were strongly concentrated in the STSd (not illustrated). A few cells extended into the STGr and also into the STSf/v. This result should be compared with OM59 LY, described below (see Fig. 18), in which an anterograde tracer injected in STSd strongly labeled axons in the medial part of area 12o.

Injections in the orbital network. Other experiments with retrograde tracer injections in restricted areas of the orbital network also demonstrated a distinct pattern of labeling in the temporal cortex that was in many ways complementary to that seen with injections in the medial network. In particular, the major connections of the orbital network were with visually related areas of the inferior temporal cortex, as well as with somatic sensory-related areas of the insula and frontal operculum.

These will be illustrated by OM67, in which the retrograde tracer FB was injected into area 11l, in the rostral orbital cortex (Fig. 10). There was almost no label in the STGr/STSd, but substantial numbers of labeled neurons were found in the STSv and STSf. In addition, a substantial number of labeled cells were found in areas Id and OPf. Some label was also found in the mid-part of cingulate area 24 (a24a′/b′ of Vogt et al., 2005).

In OM69, a large injection of LY involved areas 12r and 45/46v in the ventrolateral or inferior convexity of the prefrontal cortex (Fig. 2F). It resulted in substantial numbers of retrogradely labeled cells in many areas of the temporal, insular, and opercular cortex (STSv/f, Id, and OPf; not illustrated) that were similar to those shown after the FB injection in area 11l (Fig. 10). In addition, there were many labeled neurons in different subregions of the anterior and posterior TE (mainly in areas TEav and TEpv) and perirhinal cortex (areas 35 and 36). There were also a few cells in the medial part of the STSd.

Experiments with anterograde tracer injections in the OMPFC

Injections in the medial network. Several cases are available with anterograde tracer injections in areas of the medial network (Figs. 2A,B, 11, 12). These show that the axons from the medial network have the same distribution and organization as the temporal cortex cells described above that project to the medial network. In a typical example (OM49) an injection of BDA was made into area 25, ventral to the genu of the corpus callosum (Fig. 11). Substantial concentrations of anterogradely labeled axonal varicosities were found from the dorsal temporal pole extending about 10 mm back into the STGr and STSd. Some labeled axons also presented in the ventral edge of the insula, in agranular area Iac. Few if any axons were labeled in the auditory areas, in the STSv and TE, or in the dysgranular insula (Id) and OPf.

In other cases with anterograde tracer injections in the medial network areas, the same overall distribution of terminal labeling was seen in the temporal cortex (Fig. 12). In addition, however, there were further indications that the rostral part of the medial network projects more caudally than the more caudal part of medial network. That is, axons labeled from injections near the frontal pole were distributed in two diagonal bands that extended from the rostrodorsal part of the STGr into the STSd; the more caudal of these was distributed caudal to the fibers from other parts of the OMPFC and appeared to reach the auditory parabelt belt areas (Fig. 12A,F; injections in areas 10mr and 10o). Projections from other parts of the medial network were concentrated at the dorsal temporal pole and the adjacent part of the STGr and STSd and did not extend into the auditory areas (Fig. 12B–E; injections in areas 32, caudal 10m, 14r, 12o, and 13a). For example, in OM36 an injection in the rostrodorsal part of area 10m labeled only a few axons in the temporal pole, but two diagonal bands of labeled axons were found more caudally in the STG and STSd that extended about 20 mm caudal to the temporal pole, or approximately twice as far as the axons from area 25 in OM49 (e.g., Figs. 11, 12A).

Injections in the orbital network. Anterograde tracer injections in areas of the orbital network also labeled a pattern of axons that was similar to the distribution of retrograde neurons in OM67 (Figs. 10, 13). In case OM69, an injection of LY was made in areas 12r and 45/46v (Fig. 13). Large numbers of labeled axons were found in temporal pole area TGsts, STSv/f, areas TEav and TEpv (with many fewer or none in TEad and TEpd), areas 35 and 36, areas Id, and OPf. There were also a few labeled axons in the STSd, but these were much sparser than in the STSv/f and the other areas.

A similar pattern was seen in other cases with injections in the orbital network. Injections in areas 11l, 12m, and

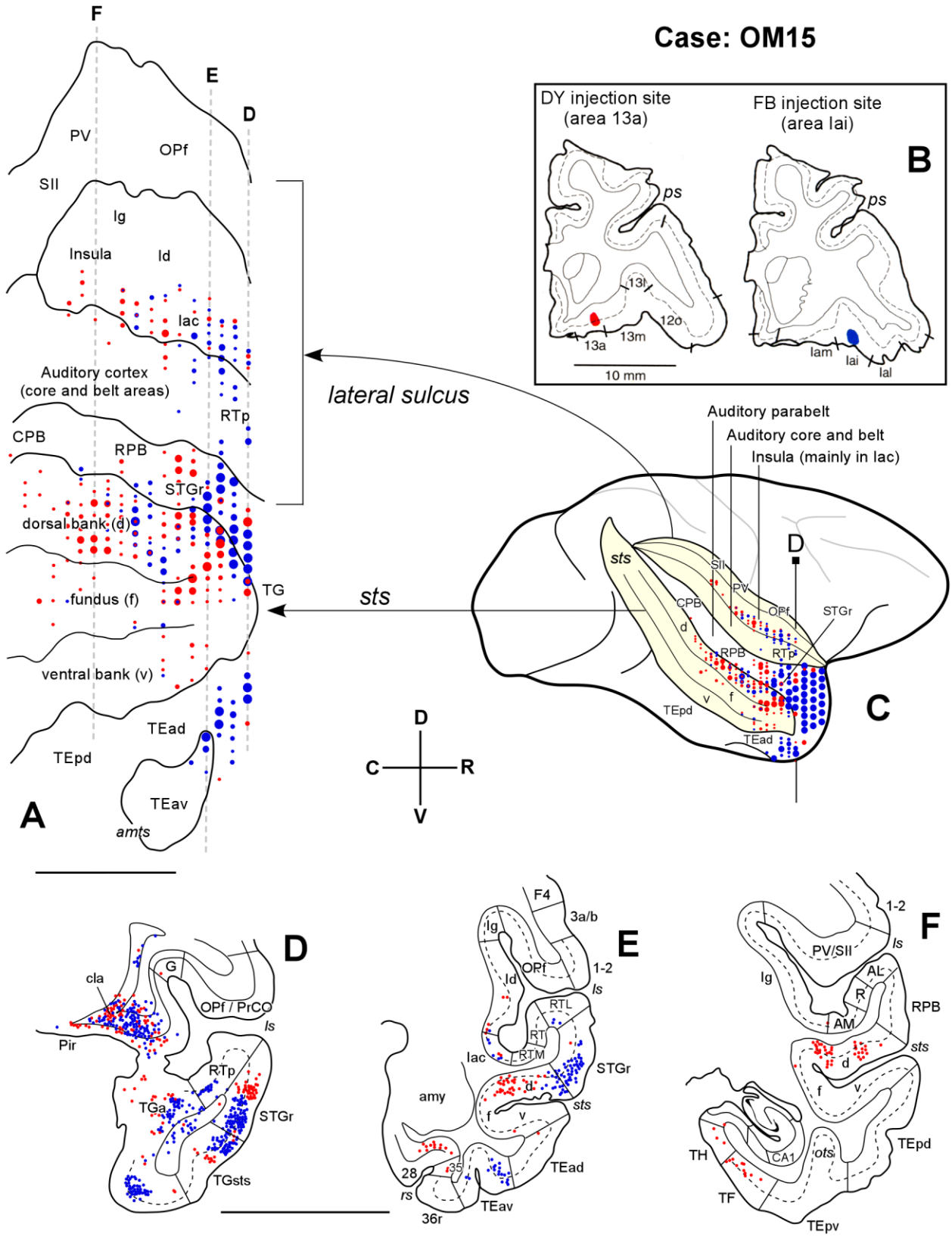


Fig. 9. **A–C:** Unfolded map and lateral view of the brain illustrating the distribution of retrogradely labeled cells in the temporal cortex and caudal agranular insula (Iac) following injections of FB into area Iai and DY into area 13a. These areas are the part of the medial network in the caudal region of the OMPFC. **D–F:** Three dashed lines in A indicate the levels of three representative coronal sections with labeling. Other details are the same as in Figures 7 and 8. Note that both injections labeled a patchy distribution of cells mainly in the STGr and STSd. The labeling does not extend into the auditory core, belt, and most of the parabelt areas. For abbreviations, see list. Scale bar = 10 mm in A, B, and D (applies to D–F).

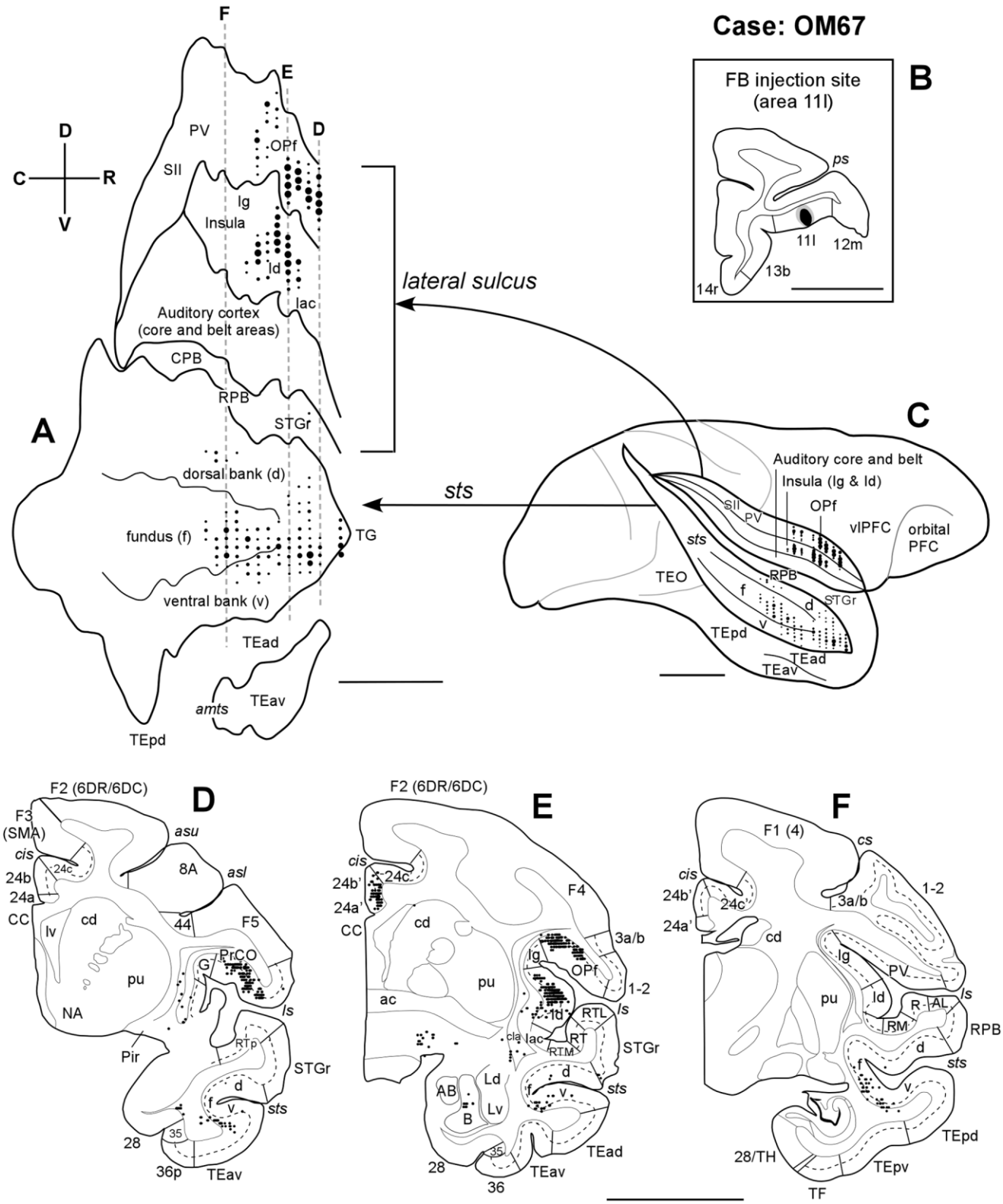


Fig. 10. **A–C:** Unfolded map and lateral view of the brain illustrating the distribution of retrogradely labeled cells in the temporal cortex, dysgranular insula (Id), and area OPf following injections of FB into orbital network area 11l. **D–F:** Three dashed lines in A indicate the levels of three representative coronal sections with labeling. Other details are the same as in Figures 7–9. Note that the labeling does not extend into the superior temporal gyrus and the auditory cortex. For abbreviations, see list. Scale bar = 10 mm in A–C and F (applies to D–F).

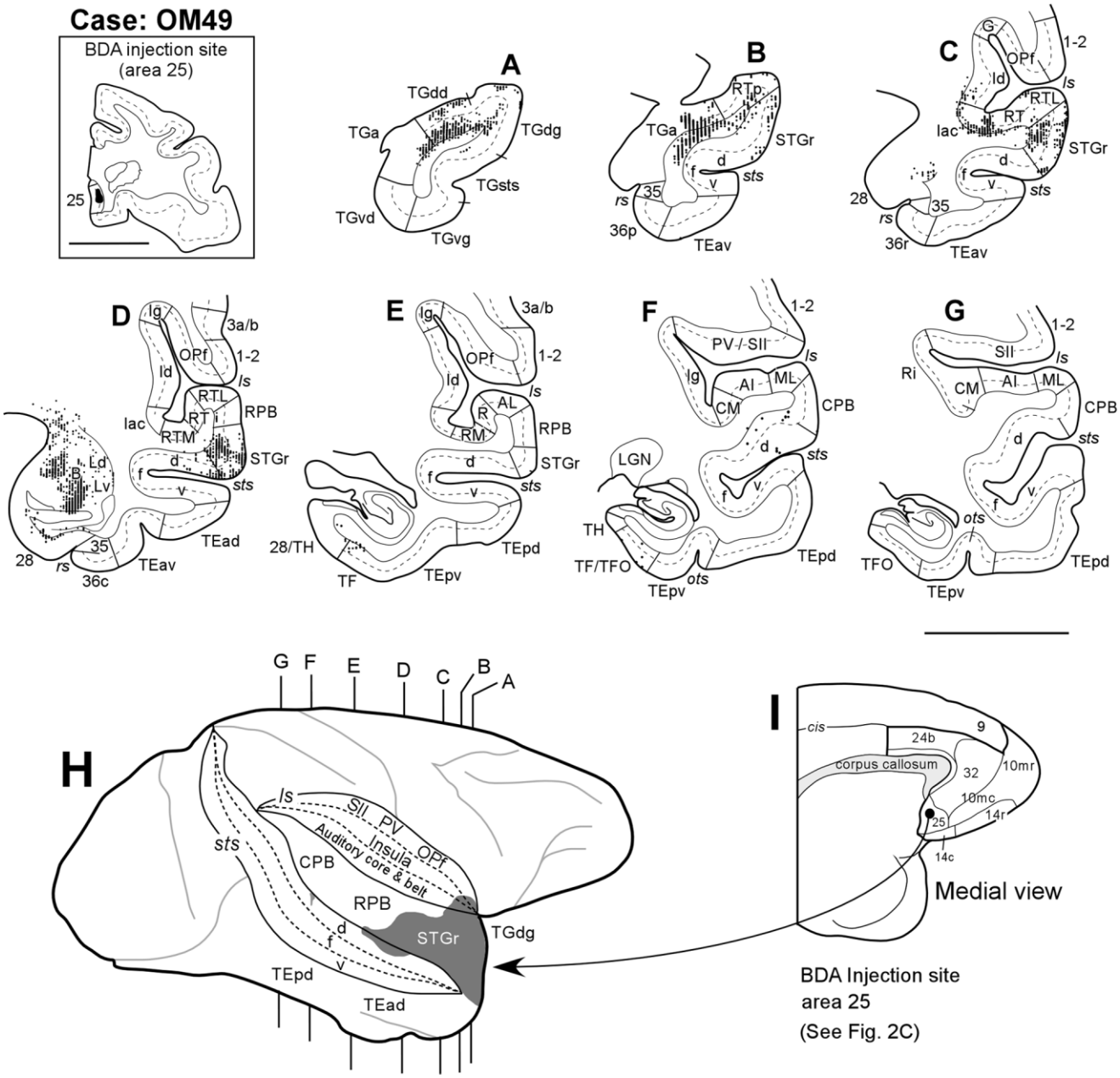


Fig. 11. Distribution of anterogradely labeled axonal varicosities in the temporal cortex following BDA injection (I) into the medial prefrontal network area 25 (**A–G**, coronal sections, black dots; **H**, lateral view of brain, gray shading). Note that the label is located in the dorsal temporal pole (TGdg, TGdd, and TGa), the STGr, and the STSd. No labeling is found in the auditory core, belt, and parabelt areas. For abbreviations, see list. Scale bar = 10 mm in top box and G (applies to A–G).

13l labeled axons in the STSv/f and Id (Fig. 14). The injections in 13l and 12m also labeled axon terminals in area TEav (Fig. 14A,B).

Experiments with retrograde tracer injections in the temporal cortex

Injections in the superior temporal cortex. Several experiments were done with injections of retrograde tracers into different rostrocaudal parts of the STG and STSd (Fig. 5A). As predicted from the injections in the OMPFC, these labeled cells were found mainly in the medial prefrontal network. In addition, other experiments had injections in the auditory belt and parabelt areas, which provided a comparison of their connections in relation to those of the STGr/STSd.

Case OM68 had two injections of DY or FB, in ventral and dorsal parts of the superior temporal cortex, respectively, at the level of the amygdala. The ventral injection (DY) was located in the caudal part of the STGr, just dorsal to the upper lip of the STS (Figs. 15B, 16B). It

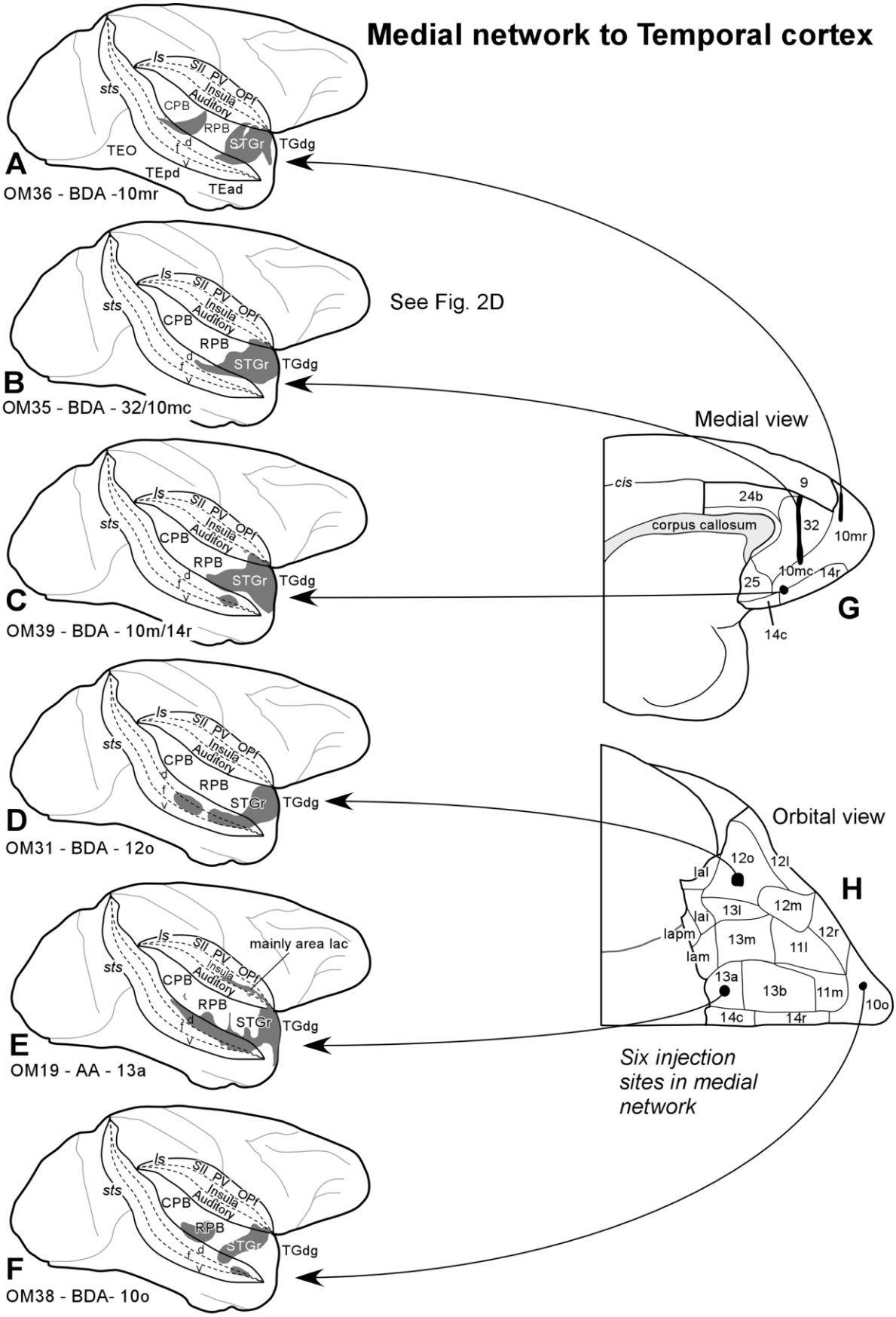


Fig. 12. **A–H:** Distribution of anterogradely labeled axonal varicosities in the temporal cortex following BDA or amino acid (AA) injections into areas of the medial prefrontal network, shown by gray shading on the lateral view of the brain. Note that in all the cases, the label is located in the dorsal temporal pole, STGr, and STSd. The labeling is also found in the auditory parabelt areas in the two cases with injections in the frontal pole (A,F). For abbreviations, see list.

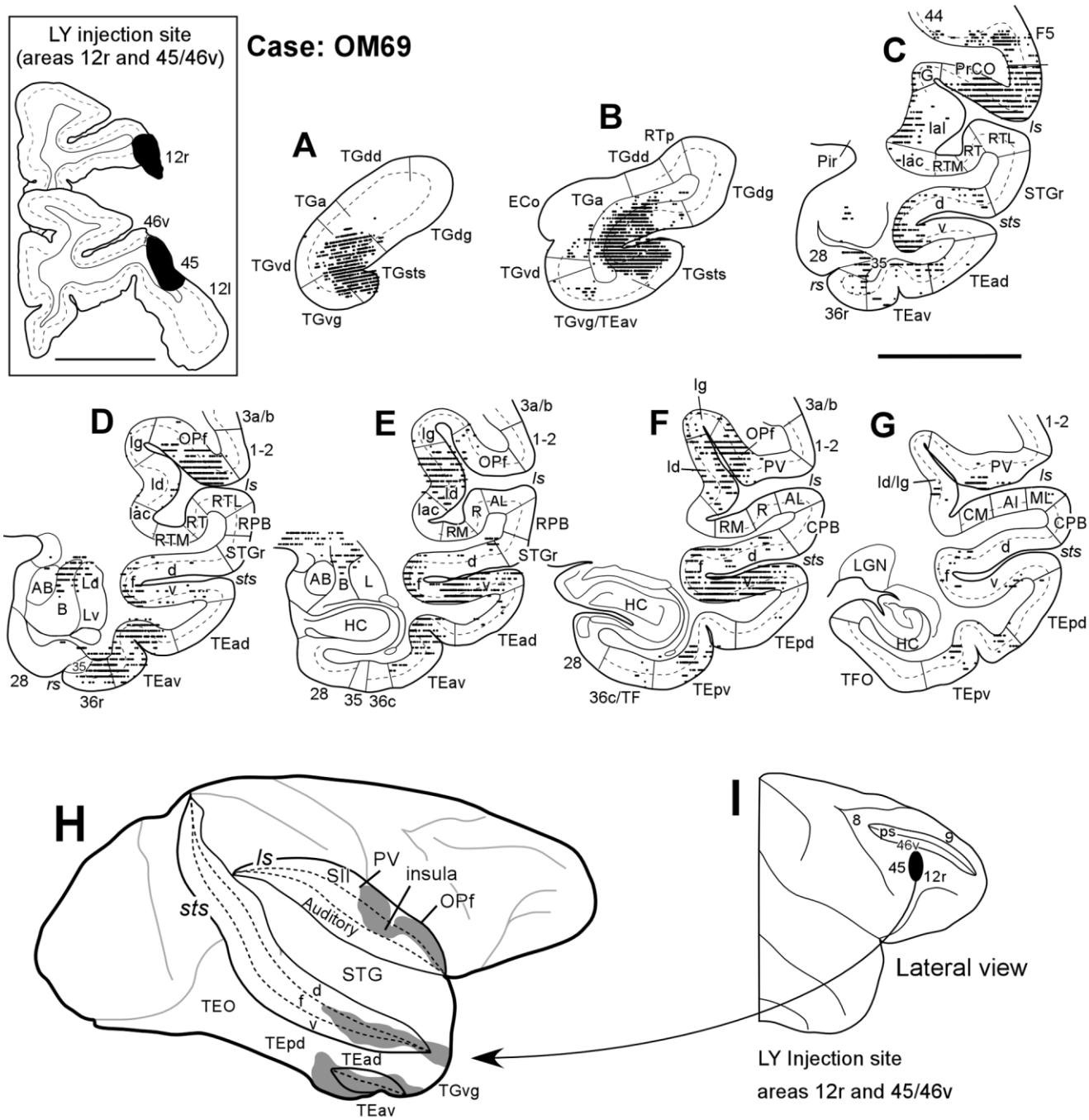


Fig. 13. **A–I:** Distribution of anterogradely labeled axonal varicosities in the temporal cortex following an injection of LY into the orbital prefrontal network area 12r, and areas 45/46v. Other details are the same as in Figure 11. Note that the label is mainly found in the TE, 35/36, STSv/f, Id, and OPf. Also note that there is no labeling in the auditory core, belt, and parabelt areas. For abbreviations, see list. Scale bar = 10 mm in top box and C (applies to A–G).

resulted in substantial numbers of retrogradely labeled cells in many areas of the medial network, including areas 10mr/c, 10o, 11m, 12o, 13a, 14r, and Iai, with smaller numbers of cells in areas 25 and 32. There were also cells in the dorsal part of area 46 (46d).

In contrast, the dorsal injection (FB) in OM68 was dorsal to the STGr, at the border between the rostral auditory belt and parabelt areas (RTL/RPB; Figs. 15C, 16C). Although the tracer FB is usually more effective than DY, many fewer cells were labeled from this injection. Those cells were distributed in restricted parts of the medial network, in areas 10mr, 13a, 12o, and Iai. There were additional cells at the border of areas 12l and 45 and in area 46d in the dorsal bank of the principal sulcus.

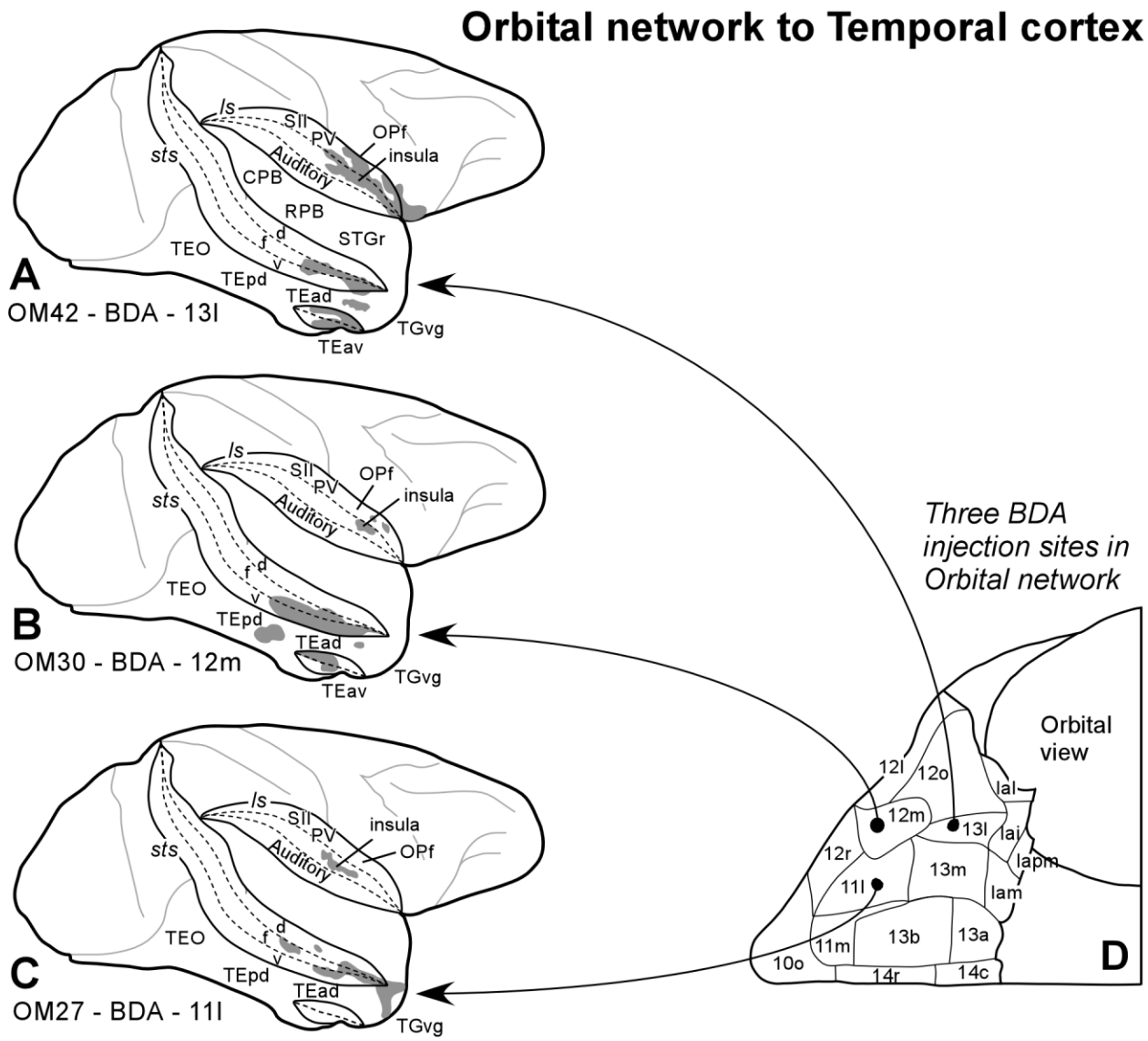


Fig. 14. **A–D:** Distribution of anterogradely labeled axonal varicosities in the temporal cortex following BDA injections into areas of the orbital prefrontal network (13l, 12m, and 11l). Other details are the same as in Figure 12. Note that the labeling is found in the TE, STSv/f, and insula after 13l and 12m injections (A,B) but only in the STSv/f and Id after 11l injection (C). For abbreviations, see list.

A similar contrast was seen when very rostral and caudal injections in the superior temporal cortex were compared. In OM59, a relatively small injection of DY was made in the rostral part of STGr, rostral to the amygdala (Fig. 15A). The labeled neurons in this case were distributed through many of the areas of the medial network, including areas 10mr/c, 10o, 25, 13a, 12o, and Iai. This contrasts with the distribution of labeled cells in OM62, which had an injection of DY in the caudal parabelt region (CPB), at the level of the lateral geniculate nucleus and hippocampus (Figs. 15D, 16D). This injection labeled almost no cells in the OMPFC, although there were cells in the rostrodorsal part of area 46. A patch of labeled cells was also found in area 45 in the ventrolateral PFC.

Injections in the inferior temporal cortex. As predicted from these experiments with tracer injections in the orbital network, injections into inferior temporal area TE resulted in transported label that was distributed in the orbital network and avoided the medial network. Three experiments with retrograde tracer injections into TEad/TEav (OM59-FB), TEav (OM71-FB), and TEpd (OM57-FB) will be presented (Fig. 17A–C). In OM59-FB, the injection was near the rostral end of TEad and appeared to overlap the border with TEav, whereas in OM71-FB, the injection was centered in TEav. In both of these cases, labeled neurons were found in areas 11l, 12l, 12m, 13l, 13m, and Ial, but virtually no cells were found in the medial network areas. Substantial numbers of labeled cells were also found in ventrolateral PFC areas 45, 46v, and PrCO (Fig. 17A,B). In OM57-FB, with an injection in TEpd, almost no labeled cells were found in the orbital cortex, except for a few cells in areas 12l and 12m and

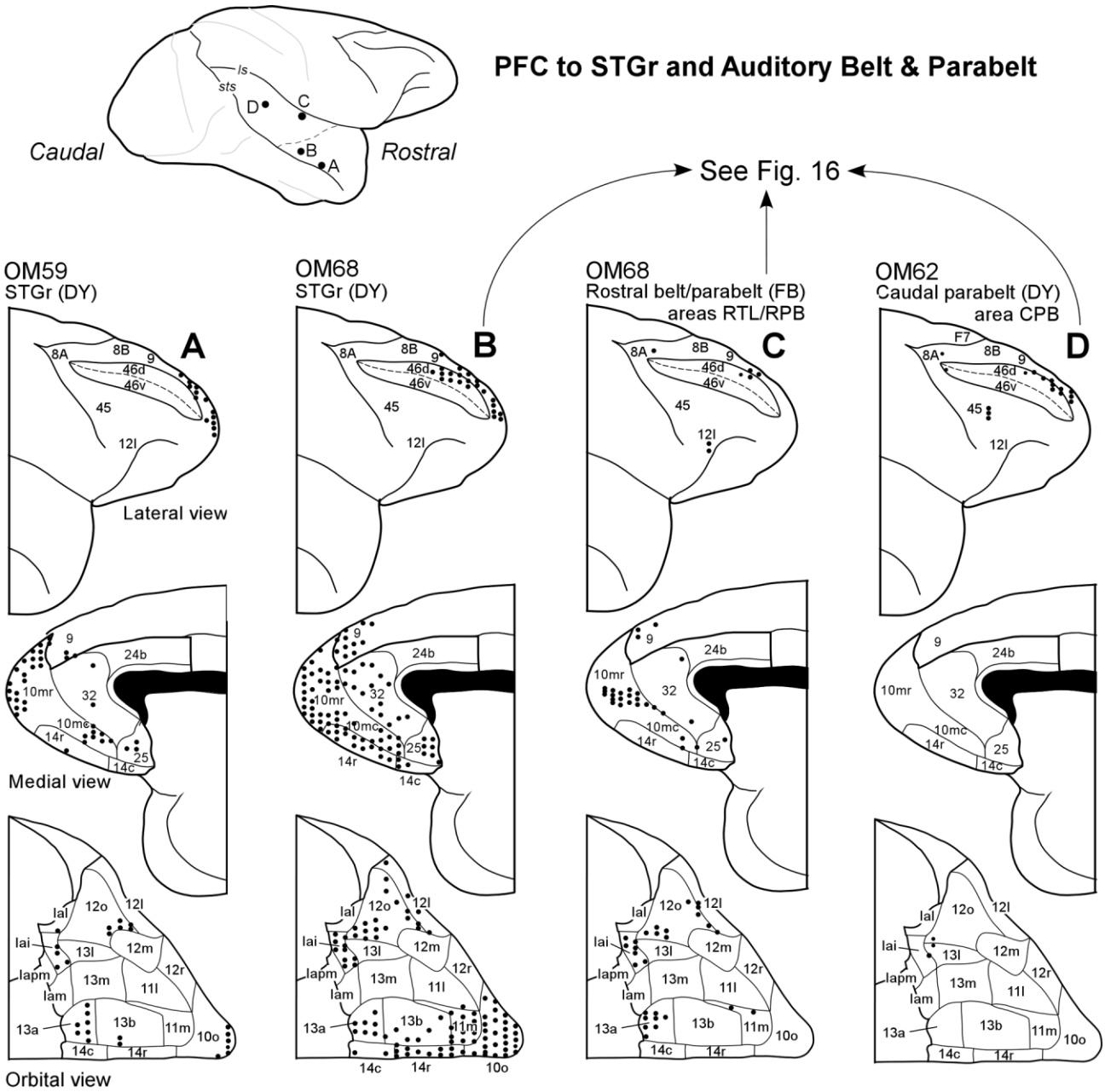


Fig. 15. **A–D:** Lateral, medial, and orbital views of the prefrontal cortex showing the distribution of retrogradely labeled neurons after retrograde tracer injections into the STGr (A,B), rostral belt/parabelt (C), and caudal parabelt (D). These surface maps are created based on the data shown in Figure 16. The locations of the injection sites are also indicated in the lateral view of the brain on the top. Note that there are many labeled cells in the medial network areas after STGr injections (A,B). For abbreviations, see list.

others in or adjacent to the claustrum, but many labeled cells were present in area 45 (Fig. 17C).

In another experiment, an injection of CTb was made in the fundus of the STS (case OM63; Fig. 5A, injection 11). Cells were retrogradely labeled in areas 12l, 12m, 12r, and 45, and there were some cells in the fundus of the principal sulcus (not illustrated). There were only a few cells labeled in areas 13m or 13l in the central part of the orbital cortex.

Experiments with anterograde tracer injections in the temporal cortex

Injections in the superior temporal cortex. Axons labeled in the frontal cortex from anterograde tracers injected into STGr/STSd were also distributed in the medial prefrontal network and in the related dorsomedial PFC (Fig. 18). In OM59, an injection of the bidirectional tracer LY was made into the rostral part of the STSd, which extended into

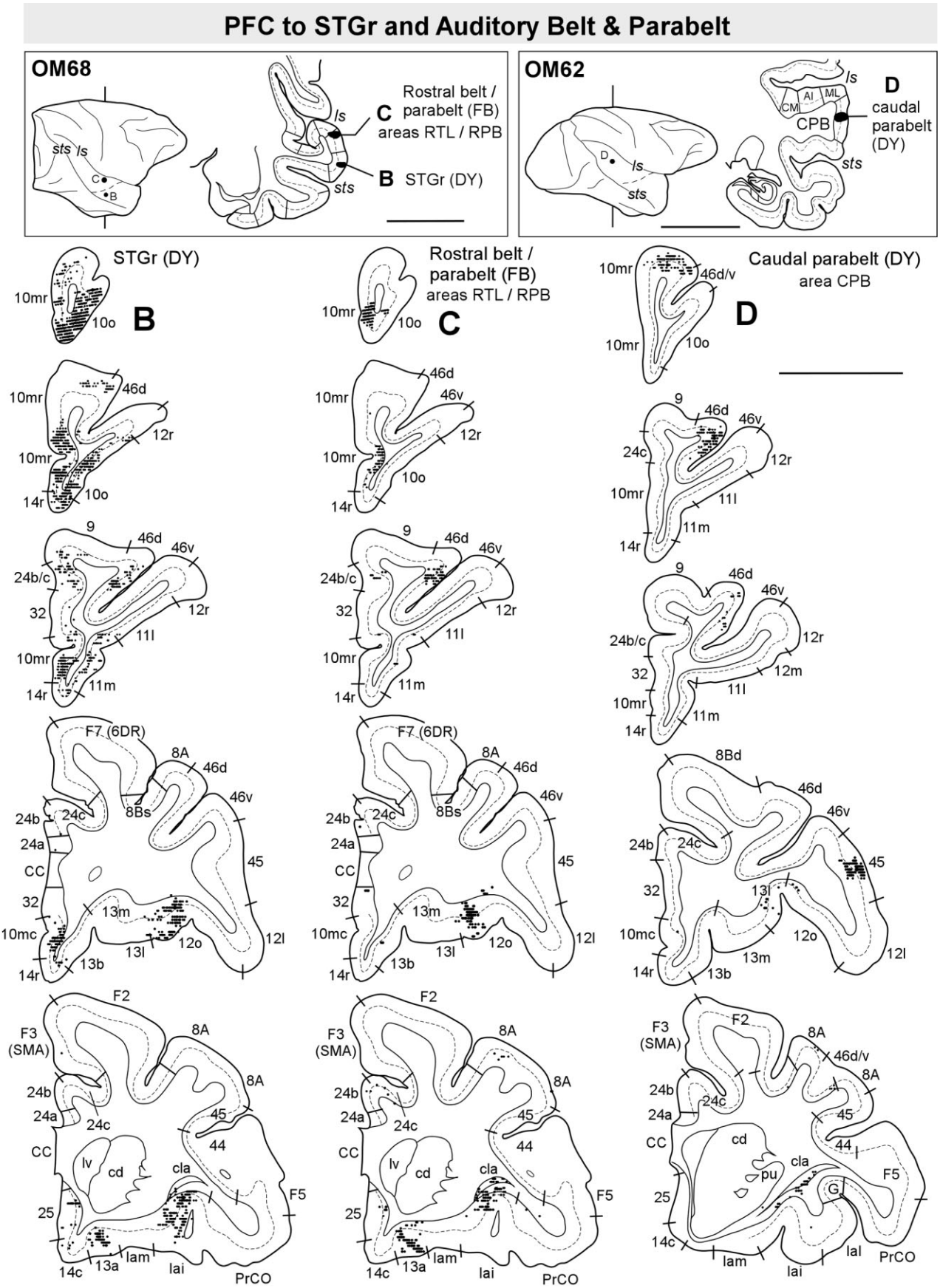


Fig. 16. A series of coronal sections showing the distribution of retrogradely labeled neurons in the prefrontal cortex after three retrograde tracer injections into the STGr (B), rostral belt/parabelt (C), or caudal parabelt (D). The locations of the injection sites are also indicated in the inset on the top. Another STGr injection site is not illustrated in this figure (but see Fig. 15A). Dashed lines indicate layer IV or boundary between layers III and V. Other details are the same as in Figure 15. For abbreviations, see list. Scale bar = 10 mm in top boxes and D (applies to B–D).

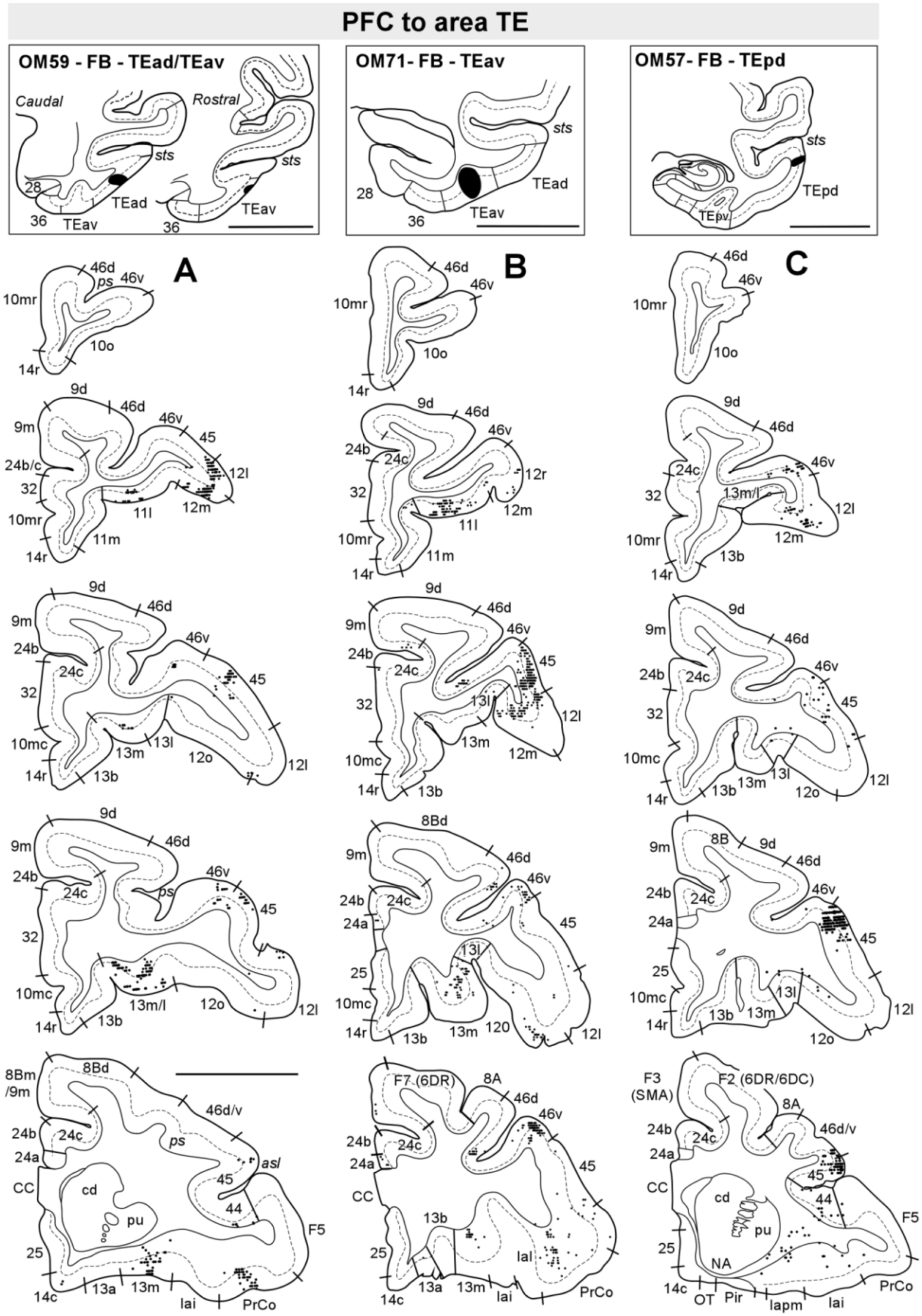


Fig. 17. **A–C:** Series of coronal sections illustrating the distribution of retrogradely labeled neurons in the prefrontal cortex after three retrograde tracer injections into different subregions of area TE. Other details are the same as in Figure 16. Note that the labeled cells are distributed in the orbital network areas and in the ventrolateral prefrontal cortex. For abbreviations, see list. Scale bar = 10 mm in top boxes and A (applies to A–C).

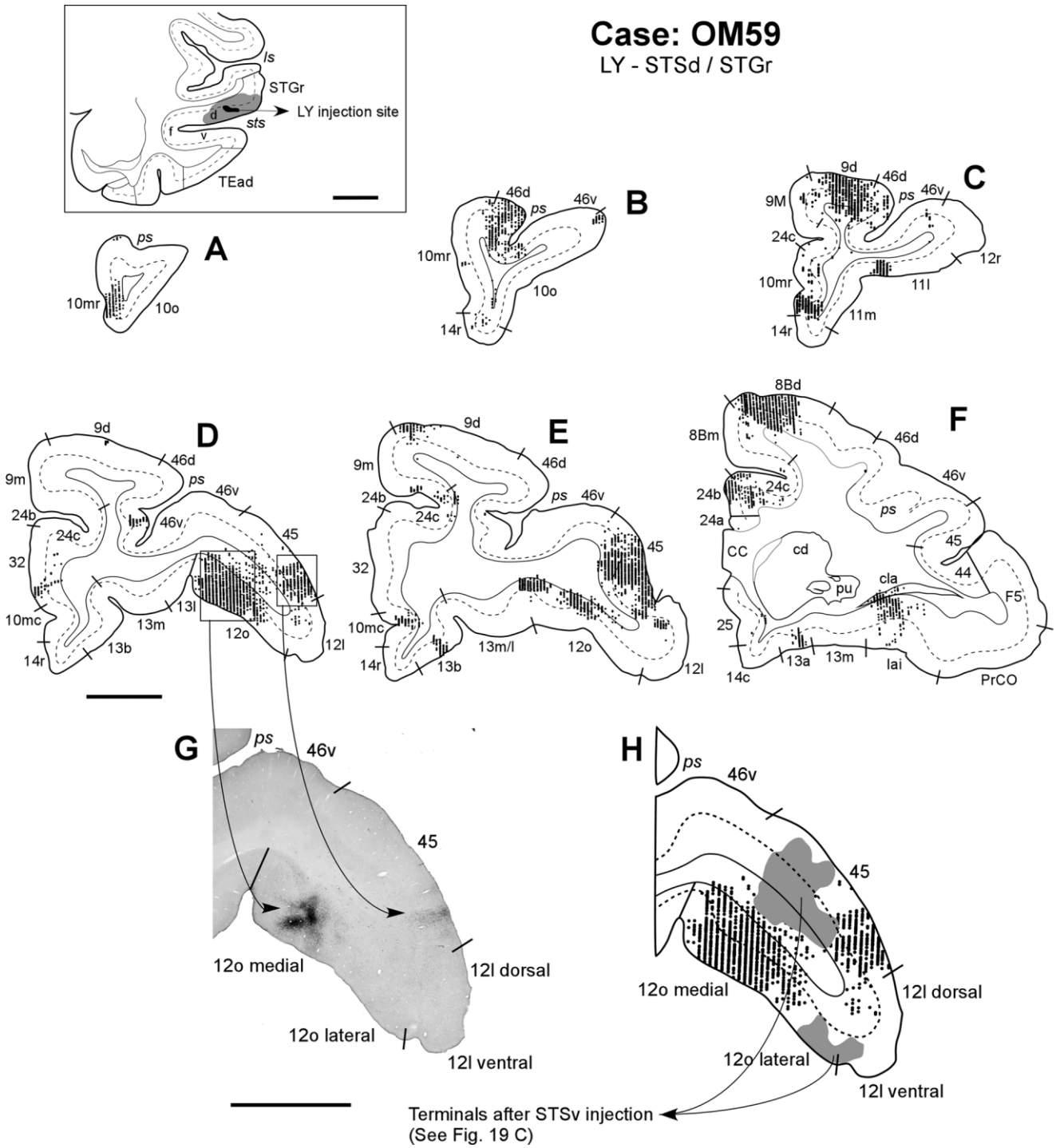


Fig. 18. **A–F:** Distribution of anterogradely labeled axonal varicosities in the prefrontal cortex following an injection of LY into the superior temporal cortex (STSd/STGr). **G:** A photomicrograph example showing the axonal labeling in areas 12o and 45 after this injection. **H:** A part of the orbital and ventrolateral prefrontal cortex (areas 12o and 45) taken from section D illustrates the axonal varicosities. For comparison, the distribution of axonal varicosities after another injection in the inferior temporal cortex (STSv; gray shading) is also indicated in these prefrontal areas in the same case (see Fig. 19C). Note that the two injections produced complementary patterns of axonal varicosities in areas 12o and 45 and other prefrontal areas. For abbreviations, see list. Scale bar = 5 mm in top box, D (applies to A–F), and G (applies to G,H).

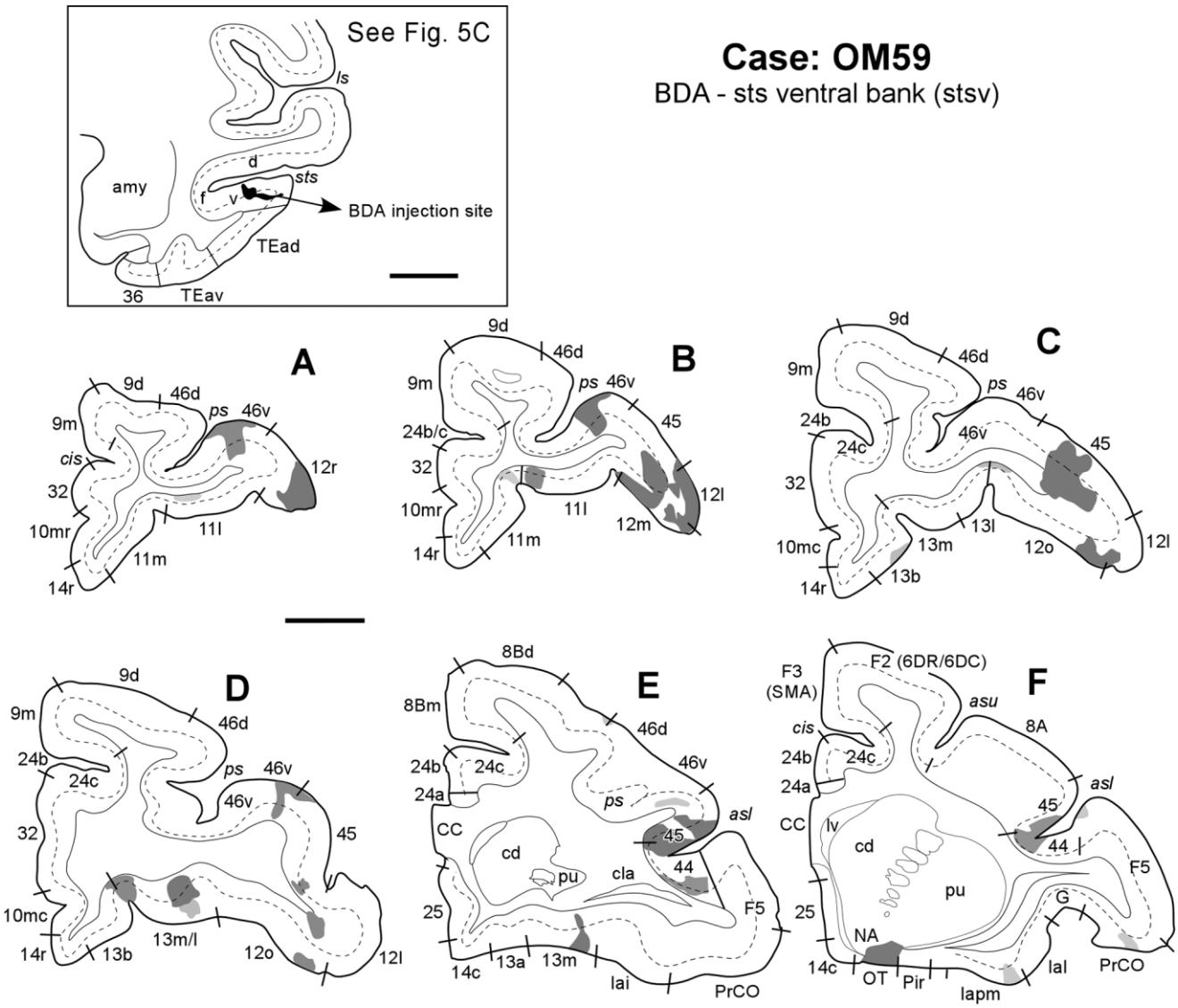


Fig. 19. **A–F:** Distribution of anterogradely labeled axonal varicosities (gray shading) in the prefrontal cortex following a BDA injection into the inferior temporal cortex (STSv). Note that the labeling in the prefrontal cortex is complementary to that related to the superior temporal cortex injection shown in Figure 18. For abbreviations, see list. Scale bar = 5 mm in top box and A (applies to A–F).

the ventral part of the STGr. Labeled axons were found in areas 10m, 14r, 24b/c, and 32 on the medial wall of the frontal lobe and in areas 9 and the dorsal part of 46 on the dorsomedial convexity. In addition, in the orbital cortex there were labeled axons in areas 12o, 13a, 13b, and Iai, which were either associated with the medial network or intermediate between the two networks. There was also a substantial plexus of labeled axons in the caudal part of area 45 in the ventrolateral PFC. This distribution of label was complementary to the distribution of labeled axons from an injection of BDA in the ventral bank of the STS in the same case (see below, Fig. 19).

In case OM68, an injection of BDA was made in the rostral auditory belt/parabelt areas, approximately at the same location as the injection of FB in the same case (Figs. 5A [injections 4, 5], 16C). In this case the pattern of axonal varicosities anterogradely labeled with BDA closely matched the distribution of cells retrogradely labeled with FB, in areas 46d, rostral 10m, 13a, and Iai (not illustrated). There were also a few labeled axons at the border between areas 12l and 45.

Injections in the inferior temporal cortex. Finally, an injection of the anterograde axonal tracer BDA into the STSv labeled axonal varicosities in several parts of the orbital network and ventrolateral PFC (Fig. 19, OM59). In the orbital network, axons were labeled in areas 11l, 12l, 12m, 12r, 13l, and 13m. In the ventrolateral PFC, there were labeled axons in area 45 and the ventral part of area 46 (46v). Area 12o, which is intermediate between the two networks, also had some labeled axons. There were no labeled axons on the medial wall or in area Iai. There was also label in the ventral putamen, the nucleus accumbens (NA), and

the adjacent olfactory tubercle (OT) at the ventral surface (Fig. 19F).

In OM71, an injection of BDA was made in area TEav (Fig. 5A, injection 9), in a very similar location to the injection of FB in the same case (Figs. 5A [injection 8], 17B). The distribution of axonal varicosities labeled with BDA closely matched the distribution of neurons labeled with FB, in areas 11l, 12m, 12l, and 13m in the orbital cortex and in areas 45 and 46v in the ventrolateral PFC (not illustrated).

DISCUSSION

This study has defined two complementary systems of connections between the OMPFC and the temporal, insular, and opercular cortex, which extend and confirm the previously defined "orbital and medial prefrontal networks" within the OMPFC itself. It is important to emphasize that the orbital and medial networks are not synonymous with cortex on the orbital or medial cortical surfaces. The networks were originally defined on the basis of local corticocortical connections, such that the areas of each network are preferentially connected to other areas of the same network and have fewer connections to the other network (Carmichael and Price, 1996). Subsequent studies confirmed the same networks, based on differential connections with the hypothalamus (Öngür et al., 1998), the periaqueductal gray (An et al., 1998), the striatum (Ferry et al., 2000), the temporal pole (Kondo et al., 2003), and the perirhinal and parahippocampal cortex (Kondo et al., 2005). The orbital prefrontal network includes most of the cortical areas on the central orbital surface, and some lateral orbital areas, but does not include all the areas on the orbital surface. In contrast, the medial prefrontal network includes not only areas on the medial wall and the frontal pole but also areas on the medial edge of the orbital surface and a small region in the posterolateral part of the orbital cortex (Fig. 1A,B).

The cortical areas connected to each of the prefrontal networks differ in their apparent function, as well as anatomically. Thus, the orbital prefrontal network is connected to several sensory-related areas (Figs. 20, 22A). These include visual association areas in the inferior temporal cortex (mainly areas TEav, TEpv, and STSv/f), and somatic sensory-related areas in the frontal operculum (OPf) and insula (Id). As shown previously, the orbital network also has connections with taste-, visceral-, and olfactory-related areas, as well as with the perirhinal cortex (areas 35 and 36) (Carmichael and Price, 1995b, 1996; Kondo et al., 2005).

In contrast to this, the medial prefrontal network is connected with area STGr/STSd, the entorhinal and parahippocampal cortex, and most parts of the cingulate cortex (Figs. 21A, 22B; Carmichael and Price, 1995a,b; Kondo et al., 2005; present results), which are not apparently sensory or motor in function (see below). The STGr/STSd region is immediately rostral to the auditory belt/parabelt areas, but there are relatively few connections between the auditory areas and either the STGr/STSd or the medial prefrontal network (Fig. 21B; see below). In addition, the medial network has specific outputs to the hypothalamus and the periaqueductal gray, which do not arise from areas of the orbital network (Öngür et al., 1998; An et al., 1998).

Definition of the medial and orbital prefrontal networks

On the whole, the original definition of the orbital and medial networks has proved to be relatively accurate as additional information has been obtained about connections of each network with other parts of the brain (An et al., 1998; Öngür et al., 1998; Ferry et al., 2000; Kondo et al., 2003, 2005; Hsu and Price, 2007). The core regions of both networks have been well established. The medial network clearly includes the medial wall, plus a region in the caudolateral orbital cortex, whereas the orbital network is best represented by areas in the central and lateral part of the orbital cortex. As expected, however, some modifications have been suggested by new results. Areas at the border of the two networks, along the gyrus rectus, can be variably assigned to the two networks, depending on the criteria being used. Areas 13a, 13b, and 14c, in particular, have been considered part of one or the other network, or as intermediate between them (see Kondo et al., 2005 for further discussion). The evidence presented in the current study suggests that these areas are most strongly associated with the medial network.

Similarly, area 12o has been considered as an intermediate area related to both networks (Carmichael and Price, 1996). In this study, area 12o as a whole was again found to have connections similar to that of both networks, but it appeared that this might reflect heterogeneity of the area and that further subdivision might be possible. Thus the medial part of area 12o has connections similar to those of the medial network, whereas the lateral part has connections similar to the orbital network. At present, however, there are not yet sufficient data to support a clear subdivision.

Finally, the small areas Iam and Iapm, in the caudal part of the orbital surface, have generally been considered part of the orbital network (Fig. 1B). In this study, however, these areas appeared to project to both area STGr and the inferior temporal cortex. This analysis is complicated not only by the small size of these areas but also by the presence of the claustrum immediately deep to them. This part of the claustrum is connected to these same cortical areas, and in this region the white matter layer between the claustrum and cortex is very poorly developed, so that claustral cells may overlap with the deep layers of the cortex (e.g., Fig. 6K).

Orbital network-related circuit

There are several previous indications that areas in the central part of the orbital cortex are related to sensory areas and receive multimodal sensory inputs. Barbas (1988) and Webster et al. (1994) both reported that the orbital and ventrolateral prefrontal cortex, including parts of areas 11, 12, 13, and 45, receive visual inputs from area TE in the inferior temporal cortex. Barbas (1988) also described somatic sensory-related projections to the orbital cortex from the insula and frontoparietal operculum, and another report has described orbital inputs from parietal area 7b (Carmichael and Price, 1995b). In addition, olfactory and gustatory inputs reach several orbital areas (Rolls and Baylis, 1994; Carmichael et al., 1994). Taken together, these data suggest that the orbital network is a sensory integration system that may be especially involved in the assessment of food stimuli (Öngür and Price, 2000).

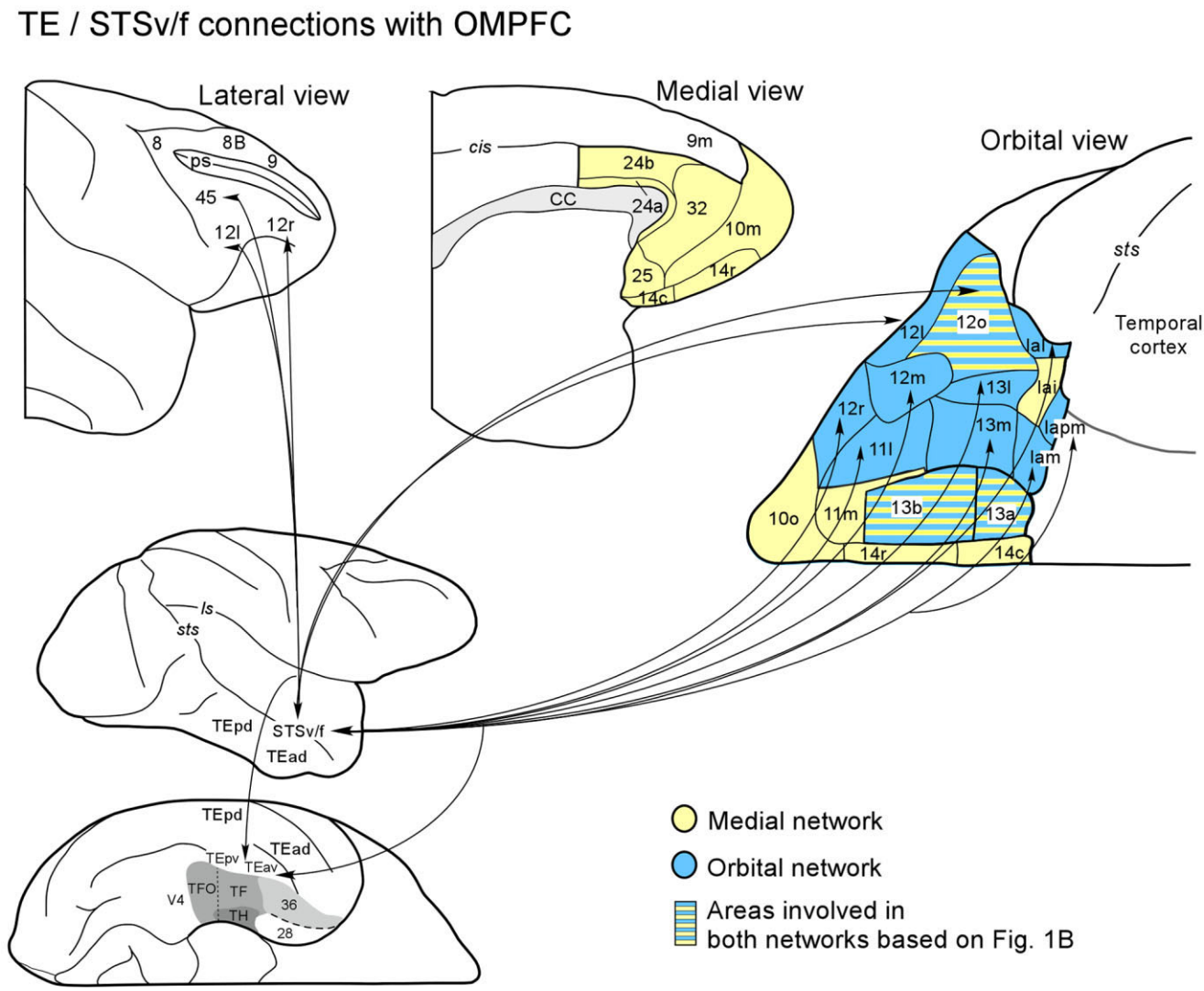
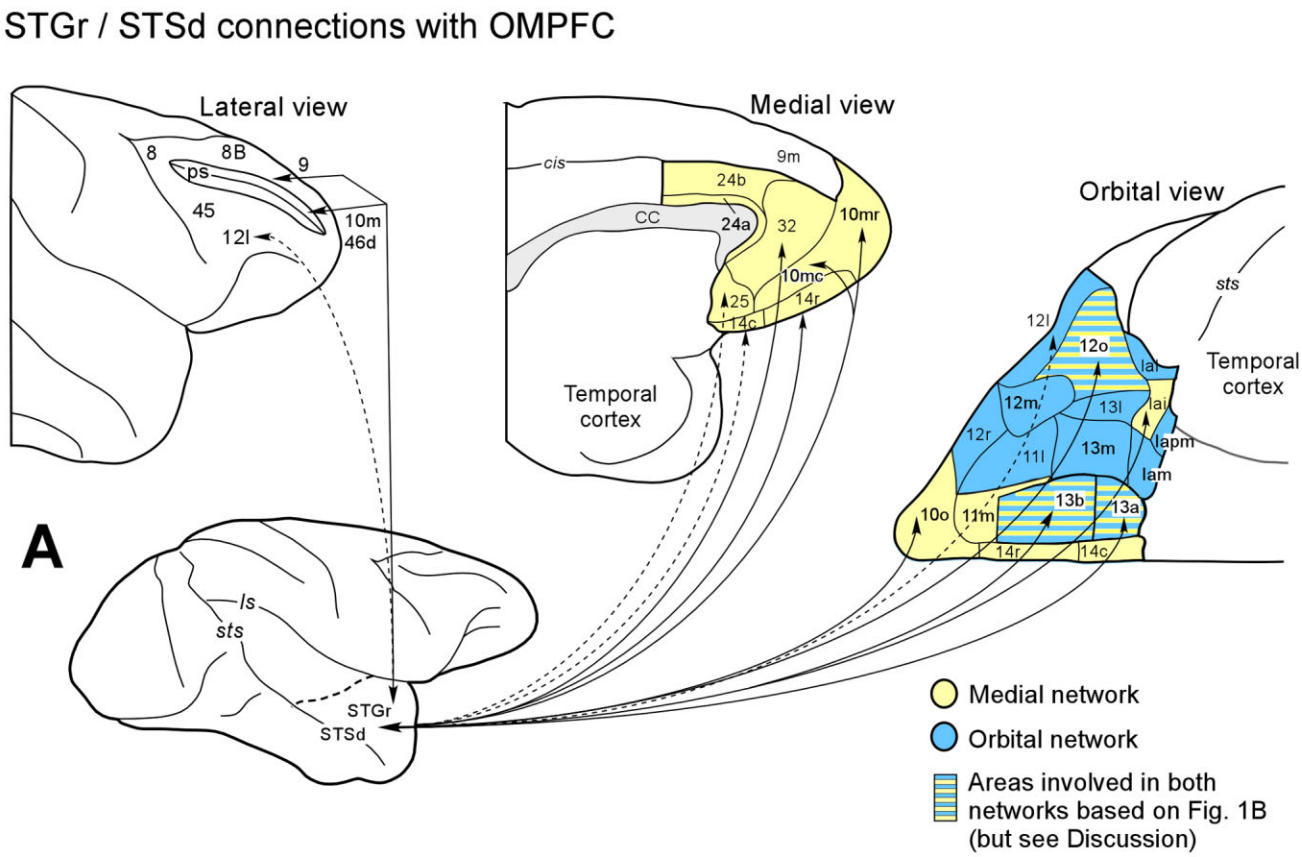


Fig. 20. Summary diagram of the connections between the prefrontal cortex and the inferior temporal cortex (area TE and STS ventral bank and fundus). These inferior temporal cortical areas are mainly connected with areas of the orbital network and area 45 in the ventrolateral prefrontal cortex. For abbreviations, see list.

Physiological studies of the orbital cortex have indeed recorded multimodal responses, mainly to food-related stimuli (Rolls et al., 1996a,b; Rolls, 2000). The responses do not simply correspond to the sensory properties of the stimuli, however, but may also reflect the affective properties or "value" of the stimuli, as well as aspects of reward (Critchley and Rolls, 1996; Schultz et al., 2000; Rolls, 2000; Hikosaka and Watanabe, 2000; Padoa-Schioppa and Assad, 2006). It appears, therefore, that the orbital network is involved in the assessment of sensory objects in relation to subsequent choices or behaviors. At the simplest level, this may involve the choice of whether or not an object should be considered as food, but it is likely that other, more complex behaviors are also coded in the orbital areas.

This study has confirmed the previous reports and also has shown other characteristics of the connections between the OMPFC and the temporal cortex. Carmichael and Price (1995b) suggested that the visual- and somatic sensory-related inputs terminated within specific areas, but the present results indicate that both sensory inputs are more widespread within the orbital network. That is, visual projections from area TE and STS ventral bank/fundus not only reach area 12l, as reported by Carmichael and Price (1995b) and Petrides and Pandya (2002), but also terminate in areas 11l, 12m, 12r, 13l, 13m, and even areas Iam/Iapm in the caudal orbital cortex. As shown by Webster et al. (1994), there are also projections from area TE to area 45 in the ventrolateral prefrontal cortex. Similarly, Carmichael and Price (1995b) indicated that the somatic sensory inputs to the orbital network were concentrated in areas 12m, 13m, and 13l, but the present results have also identified connections with areas 11l and 12r.

In addition, the origin of the sensory inputs has been better characterized. The visual-related inputs to the or-



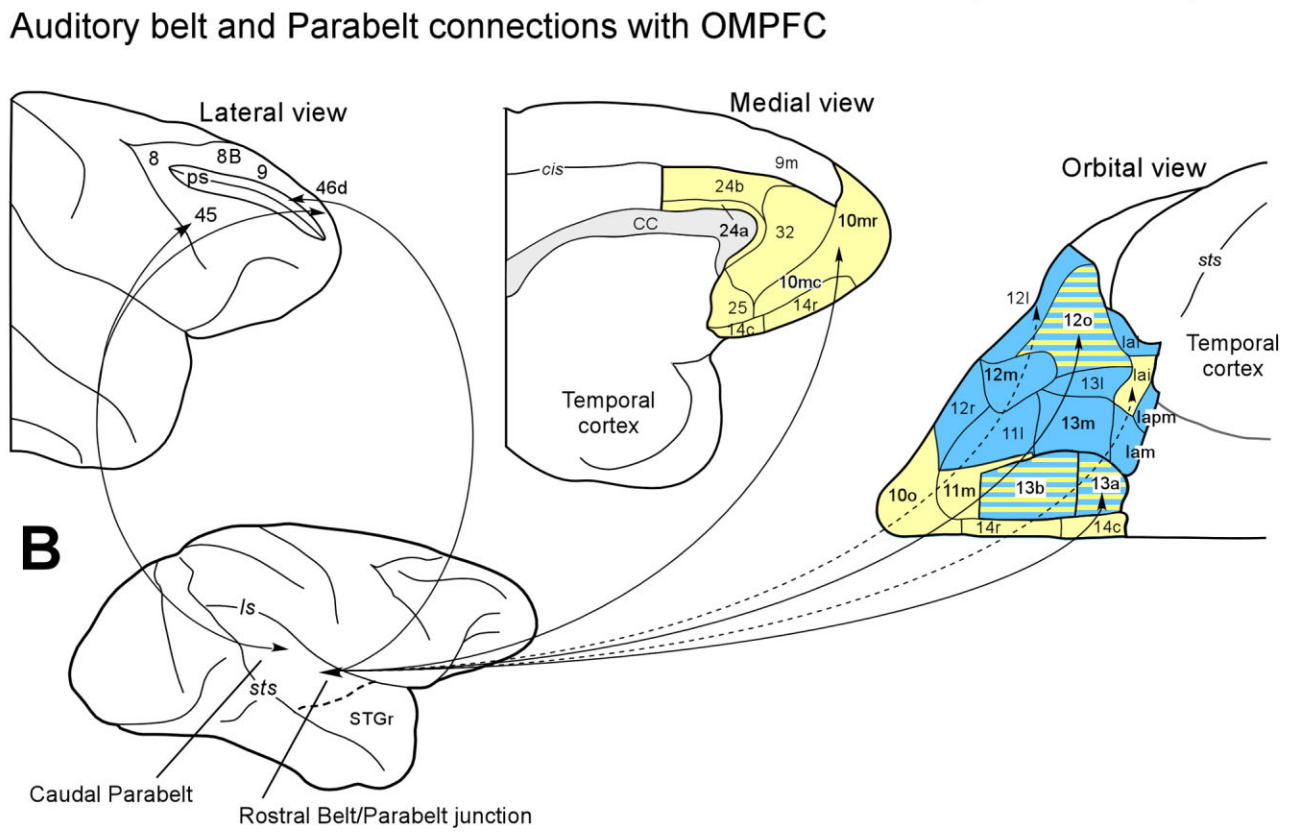


Fig. 21. **A:** Summary diagram of the connections between the prefrontal cortex and the rostral superior temporal cortex (STGr and STSd). Note that these superior temporal cortical areas are mainly connected with medial network areas, including areas on the frontal pole and dorsolateral prefrontal cortex (areas 9 and 46d). **B:** Summary of the connections between the prefrontal cortex and the auditory belt/parabelt areas. Although this auditory area is also connected with medial network areas, like the STGr and STSd, the connections are relatively much weaker. For abbreviations, see list.

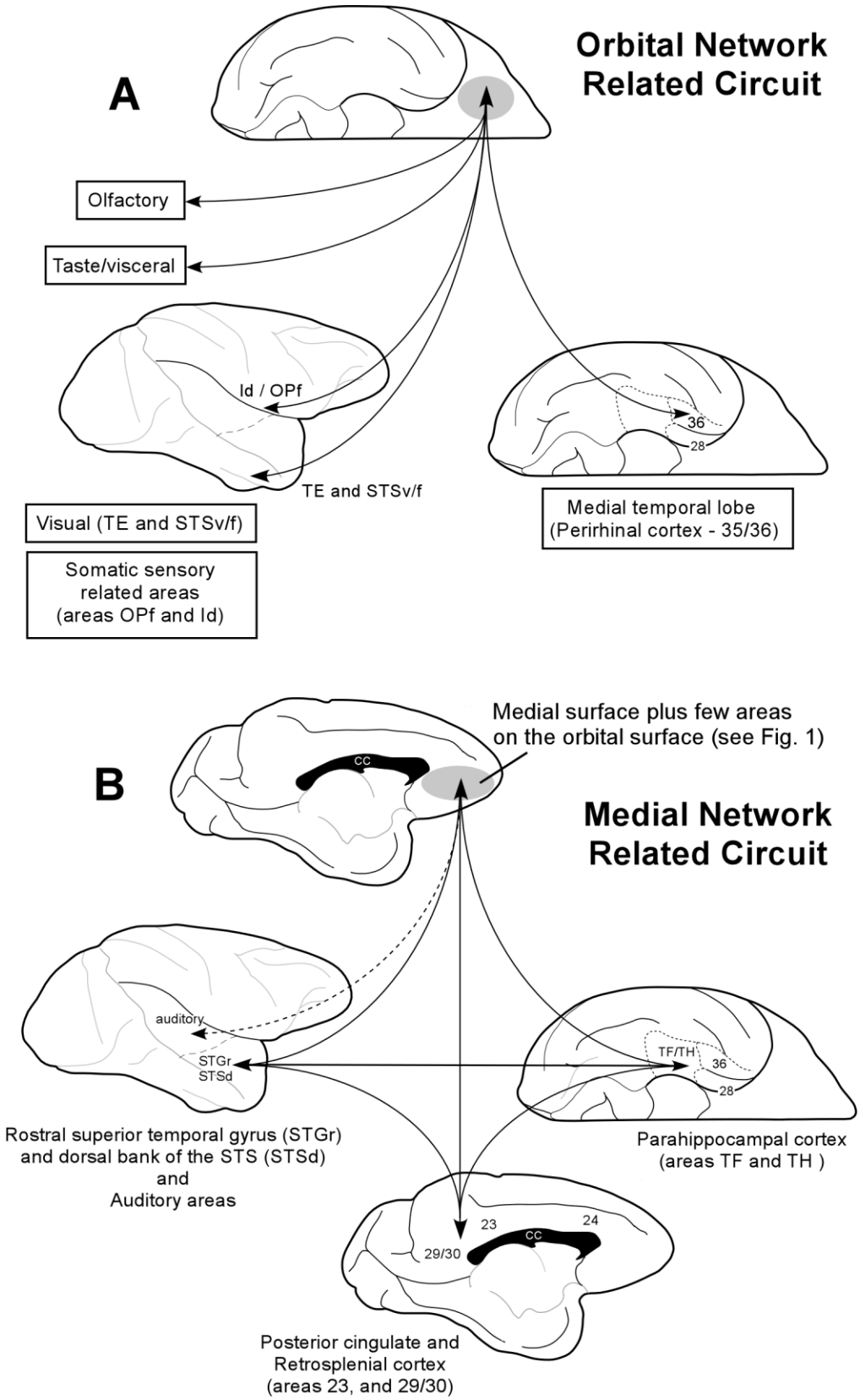


Fig. 22. **A,B:** Summary of the overall corticocortical connections of the orbital (A) and medial (B) prefrontal networks based on this and other studies (see Discussion). The orbital network is primarily connected with sensory association cortical areas representing olfaction, taste/visceral afferents, vision, and somatic sensation. The medial network, in contrast, is primarily connected to nonsensory areas (with the possible exception of the auditory cortex) including the rostral superior temporal cortex (STGr and STSd), parahippocampal cortex (TF/TH), and posterior cingulate/retrosplenial cortex (23 and 29/30), which may be involved in a self-referential or emotional system. Each of these areas is connected with the other areas as well as with the medial network. For abbreviations, see list.

bital network originate from inferior temporal area TE, but the present data also indicate that the projections do not arise equally from all parts of area TE. Many fibers to the orbital network were shown to originate in the anteroventral part of TE (area TEav) and to a lesser extent from the posteroventral part of TE (area TEpv). In addition, a substantial visual-related input to the orbital network was found from the ventral bank and fundus of the STS. In contrast, there are relatively few inputs to the orbital network from the anterodorsal part of TE (area TEad) and even fewer from the posterodorsal part of TE (area TEpd).

Previous studies of connections among these different parts of the inferior temporal area TE have also indicated that they have distinct connections with other cortical and subcortical areas. For example, a dichotomy in the connections of areas TEad and TEav with the superior temporal sulcus has been shown in Japanese macaques (Saleem et al., 2000). Area TEad connects with the dorsal bank of the rostral STS, whereas area TEav connects with the ventral bank and fundus of the rostral STS. Because the present results indicate that the dorsal and ventral banks of the STS are related to the medial and orbital networks, respectively, it would appear that area TEad may be part of a cortical system that is related to the medial network, albeit indirectly, whereas area TEav (and area TEpv) are part of the sensory circuit connected to the orbital network. It is striking that area TEad is also connected with the parahippocampal cortex (Saleem et al., 2007), which itself is related to the medial network, whereas TEav has strong connections with the perirhinal cortex (Saleem and Tanaka, 1996; Saleem et al., 2007), which is primarily related to the orbital network (Kondo et al., 2005).

Other distinctions between areas TEad and TEav are seen in their connections with the striatum, amygdala, and hippocampus. Area TEav has a strong projection to the ventral striatum (nucleus accumbens and olfactory tubercle) and to the tail of the caudate, whereas area TEad projects only to the caudate tail and has no input to the ventral striatum (Cheng et al., 1997). Within the amygdala, area TEav projects strongly to the basal nucleus, but area TEad has sparse projection to the lateral amygdaloid nucleus (Cheng et al., 1997). Finally, area TEav has moderate to strong reciprocal connections with field CA1 of the hippocampal formation, whereas area TEad has only a weak projection to the caudal part of CA1 (Saleem and Hashikawa 1998; Yukie, 2000; Zhong and Rockland, 2004; Ichinohe and Rockland, 2005).

The origin of somatic sensory inputs to the orbital network has also been restricted to areas Id and OPf, rostral to areas SII and PV (Robinson and Burton, 1980; Krubitzer et al., 1995). The nature of somatic sensory information represented in area OPf is unclear because there have been few reported physiological recordings in that areas. Many of the studies that have explored the opercular areas have used anesthetized animals, and it is possible that neurons in the OPf respond to relatively complex stimuli and are not responsive in anesthetized animals.

Lack of auditory input to the orbital network

An important exception to the multimodal nature of the sensory information coming into the orbital network is that there is little auditory input. There are projections from the rostral superior temporal gyrus into the orbital region, but these do not end in the central orbital areas that constitute the orbital network. Instead, the results of this study indicate that these terminate almost exclusively in areas associated with the medial prefrontal network. Furthermore, as discussed below, most of these inputs arise from regions rostral and lateral to the auditory belt and parabelt areas, so the auditory nature of these projections is unclear.

In contrast to the orbital network, the vlPFC (ventral to the principal sulcus on the ventrolateral frontal convexity) has been frequently reported to have connections with the auditory belt or parabelt areas (Romanski, et al., 1999a,b; Hackett et al., 1999; Petrides and Pandya, 2002). For example, in the study by Petrides and Pandya (2002), two injections in area 45 of the vlPFC (their cases 1 and 2) label connections in the auditory belt or parabelt areas, as well as in the more rostral areas TS1 and TS2 of Galaburda and Pandya (1983), which largely correspond to our area STGr. In contrast, their injections in the orbital cortex (cases 3, 4, and 5; in their area 47/12, corresponding to our areas 12o and/or 12l) label cells in areas TS1 and TS2 and/or in the inferior temporal area TE but not in the auditory belt or parabelt. Physiological recording studies also indicate auditory responses in the vlPFC (Romanski and Goldman-Rakic, 2002), where they may interact with responses to visual stimuli (Sugihara et al., 2006).

Because there are interconnections between the vlPFC and the orbital network (unpublished observations), the auditory inputs to the vlPFC may provide a pathway for some auditory input to the orbital network. A recent study that used the 2-deoxyglucose method with complex sounds provided evidence that the central and lateral orbital cortex is activated by auditory stimuli modalities (Poremba et al., 2003); a previous study also indicated activation of the orbital cortex by visual stimuli (Macko et al., 1982). Another region such as the parietal area PF (area 7b) is also reported to be activated by auditory stimuli (Poremba et al., 2003; their Fig. 2), although it has no apparent connections with the auditory system (Rozzi et al., 2006). It is likely that these regions were activated via indirect, multisynaptic pathways. In any case, the influence of auditory stimuli on the orbital network might be expected to be relatively slight, compared with those of the other modalities that have direct input to the system.

The lack of strong auditory input to the orbital network makes sense if this network is particularly involved in assessment of food and food-related stimuli, as previously suggested (Öngür and Price, 2000), because there is little auditory signal associated with food. In contrast, the vlPFC receives auditory inputs but little if any taste or olfactory inputs. It is likely that the vlPFC is also concerned with assessment of sensory stimuli (Petrides, 2005), but these may be mainly nonfood stimuli, including those with an auditory component.

Medial network-related circuit

It is striking that the medial prefrontal network is related to a distinctly different system than the orbital network. Not only is the medial network connected to largely complementary cortical regions, but these regions do not appear to have a primarily sensory function, unlike the areas connected to the orbital network. In addition to the STGr/STSd region, the medial network is interconnected with the dorsal temporal pole (Kondo et al., 2003), the caudal agranular insular area, many parts of the cingulate cortex and retrosplenial cortex, the dorsomedial pre-

frontal cortex, especially area 9 (Carmichael and Price, 1995a, 1996; present study), the entorhinal cortex, and the parahippocampal cortex (Kondo et al., 2005; present study). None of these regions is substantially connected to the orbital network.

There have been several previous indications that parts of the medial network cortex are connected to the STGr/STSd region. Jones and Powell (1970), Chavis and Pandya (1976), and Seltzer and Pandya (1989) reported connections from the superior temporal gyrus and sulcus to parts of the prefrontal cortex, although the designation of areal boundaries in these studies was not sufficiently detailed to allow analysis in terms of the orbital and medial networks. Carmichael and Price (1995b) described connections of STGr/STSd with the lateral part of the medial network, areas 13a and Iai, and with area 12o. Although all of these areas are on the orbital surface, they have consistently been found to be primarily associated with the medial prefrontal areas in the medial network (Carmichael and Price, 1996). Subsequently, Barbas et al. (1999) reported that medial prefrontal areas 9, 10, 14, 24, and 32 have common connections with the STGr/STSd region. About the same time, Romanski et al. (1999a) found that both the medial prefrontal areas 10 and 32/24 and ventrolateral area 12o have connections with the STG and STSd. Both Barbas et al. (1999) and Romanski et al. (1999a) interpreted many of these connections in relation to the auditory belt and parabelt areas in the midportion of the STG.

Most of the connections described here, and those demonstrated in the Barbas et al. (1999) and Romanski et al. (1999a) studies, however, are with areas rostral to the auditory areas, in the STGr/STSd region (areas TS1 and TS2). This region as described is adjacent to the auditory belt/parabelt regions, but there is little if any overlap with them. In all the cases reported by Barbas et al. (1999) with injections in areas 9, 10, 14, 24, 25, and 32, most of the retrogradely labeled cells were in TS1 and/or TS2, or in other rostral areas such as the dorsal temporal pole or the ventral insula (corresponding to our area Iac). Many fewer cells were labeled in area TS3, which corresponds to the rostral auditory parabelt region. In the study by Romanski et al. (1999a), case DF, with an injection in areas 24 and 32 in the medial prefrontal cortex, produced labeled cells mainly in areas TS1 and TS2 and rostral area TAa (corresponding approximately to our area STSd) but very few or no labeled cells in the rostral belt or parabelt areas. These patterns are similar to the distribution of label reported here in the STGr and STSd after the injection into the medial prefrontal cortex (e.g., Figs. 3, 4).

On the other hand, there appear to be relatively light connections between the belt and parabelt auditory areas and restricted parts of the medial network, especially areas 10m and 10o at the frontal pole. In our experiments with either retrograde or anterograde tracer injections in areas 10m and 10o, a small number of labeled cells or axons was found to extend caudally into the auditory region, although most of the label was rostral to the parabelt areas. An injection at the junction of the rostral belt and parabelt (areas RTL and RPB; OM68-FB; Fig. 16C) also labeled cells in area 10m, 12o, 13a, and Iai, although these were not as numerous as in cases with more rostral injections in the STGr (e.g., Fig. 16B). A more caudal injection in the parabelt area (area CPB; OM62-DY) labeled cells primarily in dorsal area 10m, the rostral part of area 46d, and area 45, in the lateral PFC. Similarly, experiment MR in the Romanski et al. (1999a) study, with an injection at the frontal pole, showed labeled cells in both the rostral belt and parabelt, as well as in area TS2. In a later study with injections in the belt areas, Romanski et al. (1999b) found connections with rostral area 46/10, area 45 (their area 12vl), and area 12o but not with the medial wall. The conclusion from all these experiments is that the bulk of the connections of the medial network are with areas STGr and STSd (corresponding to TS1, TS2, and TAa), which are rostral to the established auditory belt and parabelt areas. There are a few connections between auditory areas and restricted parts of the OMPFC, mainly near the frontal pole.

Kaas and his colleagues have proposed that the belt and parabelt areas are connected to STGr/STSd regions, which are in turn connected to the prefrontal cortex (Kaas et al., 1999; Kaas and Hackett, 2000). Their published experiments, however, suggest that there are only light connections between the STGr and the rostral or caudal parabelt areas. In our experiments, we also found that injections in the STGr or STSd did not label substantial connections with the belt or parabelt areas (Saleem and Price, unpublished observations), indicating that there are few auditory inputs to the STGr/STSd region. On the other hand, the 2-deoxyglucose study by Poremba et al. (2003), discussed above, reported that the STGr/STSd area could be activated by auditory stimuli. It is possible that auditory-related activity reaches this region via a multisynaptic pathway.

Part of the STGr/STSd region, especially the STSd, has also been reported to respond to polymodal stimuli, including visual and somatic sensory as well as auditory stimuli. Desimone and Gross (1979) defined a polymodal zone that surrounded the visual-related areas in the inferior temporal cortex, not only in the STSd but also in parts of the temporal pole, the perirhinal cortex, and the parahippocampal cortex. Other studies have concentrated on the mid to caudal part of the STSd (Benevento et al., 1977; Bruce et al., 1981, 1986; Baylis et al., 1987; Mistlin and Perrett, 1990; Oram and Perrett, 1996; Barraclough et al., 2005). Although the area studied by Baylis et al. (1987) overlapped the part of the STSd that is related to the medial prefrontal network, the response properties of neurons in the rostral STSd have not been well established.

In the 2-deoxyglucose studies by Mishkin and his colleagues (Macko et al., 1982; Poremba et al., 2003), both visual and auditory activation was noted in the STSd, but only auditory activation was found in the STGr. As mentioned above, these studies also indicated that most of the medial prefrontal cortex was not activated by either visual or auditory stimuli. This suggests that although neurons in the STGr/STSd area may respond to sensory stimuli, the activity it projects to the medial prefrontal network does not code sensory information as such.

The medial network is part of the default cortical system

The larger circuit that is connected with the medial prefrontal network includes not just areas STGr/STSd and Iac but also the retrosplenial/posterior cingulate cortex, the dorsolateral prefrontal cortex, the parahippocampal cortex, and the entorhinal cortex. The medial prefrontal and posterior cingulate regions are prominent parts of a cortical network that has been defined in humans with

positron emission tomography (PET), because the areas consistently decrease in activity when subjects are engaged in tasks. This pattern of activity has been referred to as a default mode of brain function (see Raichle et al., 2001; Raichle and Gusnard, 2005; Raichle and Snyder, 2007 for further detail and discussion of the basis and significance of the default mode).

The network defined by the default mode can also be visualized with functional correlation MRI (fcMRI), with the initial seed placed in the posterior cingulate cortex (Greicius et al., 2003; Fox et al, 2005). The circuit that is shown by this procedure matches many of the connections defined in this and other recent studies in monkeys. Thus, in addition to the medial prefrontal cortex and the posterior cingulate/retrosplenial areas, the default system shown with fcMRI includes the dorsal prefrontal cortex, the parahippocampal cortex, and an area in the rostral temporal cortex. The rostral temporal area is in the middle temporal gyrus, but it is possible that this corresponds to the STGr/STSd, because the middle temporal gyrus in humans appears to represent an expansion of the cortex that is located in and around the STS in monkeys, as the visual association areas in humans are moved ventrally onto the fusiform gyrus (Tsao et al., 2003; Denys et al., 2004; Orban et al., 2004). In addition, fcMRI shows another area in the posterior parieto-occipital cortex, which does not appear to correspond to any cortical region connected to the medial network.

The defining characteristic of the default network, that it shows relatively more activity when subjects are at rest than when they are engaged in externally directed tasks, suggests that it is involved in self-referential functions, when attention is focused within the individual. Evidence for this has been obtained by studies that used self-referential tasks, compared with externally directed tasks (Gusnard et al., 2001; Gusnard, 2005; Moran et al., 2006). Emotion is an obvious self-referential function, and there is substantial evidence that the medial prefrontal cortex and related structures are involved in control of emotion and are dysfunctional in mood disorders (Drevets et al., 1997, 1998; Mayberg et al., 1999, 2005). Another part of the default system, the dorsal prefrontal cortex, may be involved in non-emotional self-referential tasks, such as keeping track of recent actions and the role that the individual played in them (Petrides, 2005). A major unanswered question is what role the STGr/STSd region may play in this system.

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