Temporocingulate Interactions in the Monkey

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The cingulate gyrus has long been considered to be part of the limbic lobe (Broca, 1878) and was later incorporated into a medial circuit that formed the substrate for emotion (Papez, 1937). With the advent of modern tract-tracing methods, MacLean (1990) developed the concept of the limbic system, incorporating the amygdala and septum along with the cingulate gyrus. The circuitry of this system expanded greatly with subsequent connection studies.

Based on cytoarchitecture, connections, and functional analyses, the cingulate gyrus is comprised of four regions: anterior cingulate cortex (ACC), midcingulate cortex (MCC), posterior cingulate cortex (PCC), and retrosplenial cortex (RSC). Although all a part of the cingulate gyrus, these regions are not uniform and can be further subdivided, for example, into dorsal and ventral parts of the PCC (Shibata and Yukie, 2003). In functional terms, the cingulate cortex plays key roles not only in emotional and motivational processes but also in autonomic responses (Kaada *et al.*, 1949; Nishijo *et al.*, 1997) and higher cognitive processes, such as attention, error detection, motor activity, social behavior, conflict, and different types of memory (Smith, 1945: Mirsky *et al.*, 1957; Gemba *et al.*,1986; Valenstein *et al.*, 1987; Posner *et al.*, 1988; Grasby *et al.*, 1993b).

The temporal lobe transmits information from all sensory association cortical areas and has robust interactions with many limbic structures, including the amygdala and hippocampus. As such, the temporal lobe is involved in emotion, motivation, memory, and learning and the cingulate cortex has been implicated in aspects of these particular functions including auditory-verbal memory and memory of visual episodic events. Clinical studies have demonstrated that damage to the left RSC and the adjacent PCC or splenial tumors

involving RSC result in amnesia, more specifically auditory-verbal memory impairment (Valenstein *et al.*, 1987; Rudge and Warrington, 1991). Functional imaging studies showed that auditory-verbal long-term memory tasks activated the RSC as well as prefrontal cortex, precuneal cortex, and the hippocampus (Grasby *et al.*, 1993a, 1993b). Another study observed that activation of the left RSC and left prefrontal cortex was associated with encoding of auditory episodic memory but not with retrieval from episodic memory (Fletcher *et al.*, 1995). These facts together suggest that the PCC and RSC interact with auditory and episodic memory systems and suggest that the posteroventral region of the posterior cingulate gyrus, also called the caudomedial lobule (CML; Goldman-Rakic *et al.*, 1984), might be critical for auditory-verbal memory.

Goals of This Chapter

We will review temporal lobe interactions with the cingulate gyrus from the perspective of the cytoarchitectonic organization of monkey cingulate cortex as discussed in Chapter 3. The overall goal is to propose a structural basis for functional processes in which the PCC plays a central role. The specific goals include the following:

1　Evaluate medial temporal lobe projections from the amygdala, hippocampus, and temporal pole, commenting on their relationship to memory functions.

2　Review temporal neocortical connections involved in auditory function of the PCC and auditory memory function.

3　Describe the medial cortical connections with the PCC and RSC.

4　Assess the divisions of area 23 in the dorsal/ventral dichotomy in terms of cortical connectivity.

Medial Temporocingulate Interactions

The medial temporal cortex and sub-cortical regions referred to in this chapter occupy the ventromedial region of the temporal lobe. This region contains perirhinal areas 35 and 36, anterior parahippocampal cortex (entorhinal cortex, area 28; Brodmann, 1909), posterior parahippocampal areas TF and TH (von Bonin and Bailey, 1947; parasubiculum and presubiculum), hippocampal formation (dentate gyrus, Ammon's horn, and subiculum), and the amygdala in the ventromedial part of the temporal lobe. In recent anatomical studies, the terminology and delineations for the parahippocampal and perirhinal cortices have varied (Suzuki and Amaral, 1994, 2003; Blatt and Rosene, 1998; Boussaoud *et al.*, 1991). In this chapter, we use the terminology and delineations of Yukie (2000) to describe the organization of the medial temporal lobe.

Amygdala

It is well known that the amygdala is functionally involved in emotion, motivation, and social interactions (Klüver and Bucy, 1937, 1939; Adolphs *et al.*, 1995; Chapters 8 and 9), receives information from all sensory modalities, and interconnects directly with widespread cortical areas (Aggleton *et al.*, 1980; Turner *et al.*, 1980; Amaral and Price, 1984; Iwai and Yukie, 1987; Yukie, 2002). In the cingulate cortex, areas 24, 25, and 32 of the ACC connect reciprocally with the amygdala, while the PCC and RSC do not (Baleydier and Mauguire, 1980; Porrino *et al.*, 1981; Van Hoesen, 1981; Amaral and Price, 1984; Amaral *et al.*, 1992). The amygdalocingulate projections originate mainly from the lateral basal (LB), medial basal (MB), and accessory basal (AB) nuclei, as shown in Figure 6.1 (left). These projections terminate in layers I and II in all cytoarchitectonic subdivisions (a, b, c) of area 24 (Vogt and Pandya, 1987). Area 25 has terminations in superficial layers, similar to those in area 24, but also has deeper terminations at the border of layers III and V (Vogt and Pandya, 1987). Regarding the connections of the MCC with the amygdala, Vogt *et al.* (2003) suggested that the anterior MCC receives amygdala input, although it is less than that which arises in the pregenual cortex (Vogt and Pandya, 1987). Earlier studies employing large injections of anterograde tracers into the amygdala demonstrated that the amygdala projection to the ACC extended to areas a24´ and p24´ (Porrino *et al.*, 1981; see Amaral *et al.*, 1992 for a review), although such terms were not used at that time. Thus, amygdalocingulate projections originate from the LB, MB, and AB nuclei of the amygdala and terminate in areas 24, 25, and 32 of the ACC, extending to areas a24´ and p24´ of MCC.

Regarding the projections to the amygdala from the ACC, early studies indicated that projections from areas 24 and 25 terminated in the LB nucleus and magnocellular part of the AB nucleus (Pandya *et al.*, 1973; Baleydier and Mauguire, 1980; Van Hoesen, 1981). Area 32 projects only to the magnocellular part of the AB (Van Hoesen, 1981). In addition, a recent study, in which cortical input to the lateral (L) nucleus was examined with retrograde tracers, indicated the presence of sparse to moderate input to the L nucleus from areas 24, 25, and 32 (Stefanacci and Amaral, 2000). Among those areas, the largest number of labeled cells was in area 25. In the L nucleus, the dorsal and dorsal intermediate subdivisions appear to receive somewhat more robust cingulate input than the other subdivisions within the L nucleus. Stefanacci and Amaral (2002) also had cases with tritiated-amino-acid injections into each of areas 24 and 25 and reported that area 24 had heavy
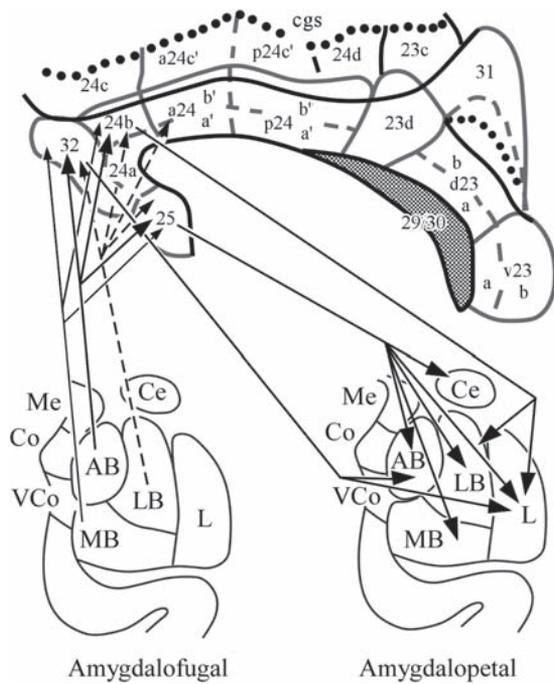
Fig. 6.1 Amygdalocingulate connections in the monkey. The ascending amygdalofugal pathways are shown with thin and dashed lines, while amygdalopetal pathways are shown with large arrows. The primary interactions of the amygdala is with the ACC and the anterior MCC areas a24a´/b´. It is striking that the PCC and RSC are free of amygdalar connections. The cytoarchitectural map in this and subsequent figures is from Vogt et al. (2005). Abbreviations for amygdala nuclei: AM, accessory basal; Ce, central; Co, cortical; MB, medial basal; Me, medial; L, lateral: LB, lateral basal; VCo, periamygdaloid also called the ventral cortical nucleus.

projections to the LB and a weak projection to the dorsal part of the L nucleus. Area 25, on the other hand, had heavy projections to the AB nucleus, moderate projections to the intermediate and parvocellular parts of the basal nucleus (LB and MB nuclei), and sparse projections to the L nucleus (Fig. 6.1, right).

Finally, observations in the cat show that area 25 projects to the central (Ce) nucleus. The cingulate projection to the Ce nucleus was described in early studies that used isotope injections into the cingulate vocalization subregion in squirrel monkeys (Smith, 1945; Müller-Preuss and Jürgens, 1976; Chapter 15). This subregion is located in the cingulate sulcus and apex of the anterior cingulate gyrus of ACC.

Subicular complex and the hippocampus

In general, the subicular complex has connections with widespread regions of the cingulate cortex, but the MCC is largely devoid of such connections. The subiculum proper, including the prosubiculum, projects to areas 24 and 25, and areas 29 and 30 of the RSC (Vogt and Pandya, 1987; Barbas and Blatt, 1995; Insausti

and Muñoz, 2001; Kobayashi and Amaral, 2003). Since retrograde tracer injections into area 30 of the RSC did not label neurons in the subiculum (Morris et al., 1999), this suggests that the subicular projection to RSC is primarily directed to area 29 rather than area 30. Projections from the subiculum are stronger to the RSC than to the ACC (Vogt and Pandya, 1987), and none terminate in the MCC, as shown in Figure 6.2. It is unlikely that area 32 of the ACC, area 24´ of the MCC, or areas 23 or 31 of the PCC receive input from the subiculum (Rosene and Van Hoesen, 1977; Vogt and Pandya, 1987; Barbas and Blatt, 1995). Area 29 receives input from the caudal half of the subiculum, while areas 24 and 25 receive input from the rostral part. Still, no study has indicated the presence of cingulate projections back to the subiculum (Pandya et al., 1981; Vogt and Pandya, 1987; Morris et al., 1999; Chiba et al., 2001).

Field CA1 of the hippocampus projects to the cingulate gyrus, especially to ACC areas 24, 25, and 32, as shown in Figure 6.2 (Vogt and Pandya, 1987; Arikuni et al., 1994; Barbas and Blatt, 1995; Insausti and Muñoz, 2001). Areas 25 and 32 received additional input from subfield CA1´ (Barbas and Blatt, 1995; Insausti and Muñoz, 2001). In contrast, area 29 of the RSC does not receive input from area CA1 or CA1´, although it receives input from the subiculum.

The presubiculum has topographically organized reciprocal connections with the cingulate cortex. The caudal part of the presubiculum projects to areas 29/30 and 23 (Insausti and Muñoz, 2001; Kobayashi and Amaral, 2003). By contrast, the rostral part of the presubiculum, and also the parasubiculum, sends sparse fibers to the anterior cingulate areas 25 and 32 (Barbas and Blatt, 1995; Insausti and Muñoz, 2001). Regarding the cingulopresubiculum projections, it has been observed that dorsal area 23 (d23) projects to the presubiculum,
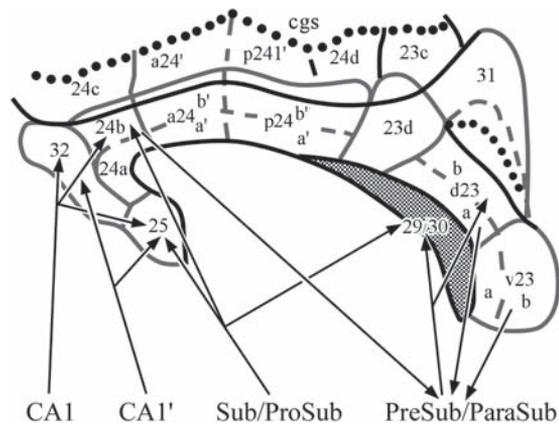

Fig. 6.2 Summary of cingulate connections with the hippocampal formation [CA1, CA1´, subiculum (Sub), and prosubiculum (ProSub)] and the parahippocampal presubiculum (PreSub) and parasubiculum (ParaSub).

while areas 24, 25, and 32 of the ACC do not (Pandya *et al.*, 1981; Morris *et al.*, 1999; Chiba *et al.*, 2001). Our recent anterograde tracing experiments using biotinylated dextran amines (BDA; anterograde and retrograde tracer) and retrograde tracing experiments using fast blue injected into ventral area 23 (v23) or area 24 demonstrated that area v23 sends substantial numbers of fibers to the presubiculum and parasubiculum, while area 24 sends only a few fibers to the anterior part of the presubiculum and parasubiculum. Morris *et al.* (1999) suggested that isotope injections of anterogradely transported amino acids into the posteroventral part of area 30 labeled fibers in the presubiculum and parasubiculum, however, the injection also involved area v23, precluding a clear interpretation by itself.

Parahippocampal Gyrus: Entorhinal Cortex

The entorhinal cortex is at a relay position between sensory association cortices and the hippocampal formation. It receives inputs directly or indirectly via perirhinal and posterior parahippocampal cortices from widespread sensory association cortices and sends information to the hippocampal formation. At the same time, it receives hippocampal output and sends it back to association cortex (Van Hoesen, 1982).

There appears to be weak reciprocal connections between the entorhinal cortex and the cingulate gyrus. Such connections are summarized in Figure 6.3. In many studies with injections of the retrograde tracer horseradish peroxidase (HRP; conjugated with wheat germ agglutinin to enhance sensitivity; WGA-HRP) and fluorescent dyes, the PCC, RSC, and ACC had some labeling originating from the entorhinal cortex (Baleydier and Mauguiere, 1980; Arikuni *et al.*, 1994; Bachevalier *et al.*, 1997; Kobayashi and Amaral, 2003; Muñoz and Insausti, 2005).

A study with injections of the retrograde tracers, choleratoxin B subunit, fast blue, and diamidino yellow into the PCC and RSC demonstrated that areas d23 and v23 had substantial projections from the entorhinal cortex, but retrosplenial areas 29/30 received only a weak projection (Yukie *et al.*, 2002). In addition, the MCC area 24′ receives input, though not much, from the entorhinal cortex (Yukie *et al.*, unpublished data). The entorhinal cortex also projects to area 24c (Morecraft and Van Hoesen, 1998), but little to area 31 or 23c (Morecraft *et al.*, 2004). Thus, the entorhinal cortex provides projections to areas 24, 25, 32, d23, v23 a24′, p24′, 24c′, and 29/30, but not to area 31 or 23c of PCC (Fig. 3.2). The neurons that originate these projections reside in layers V or VI of the entorhinal cortex, and their laminar terminations in cingulate cortex are in layers II, III, and V. It is unclear whether area 23d has entorhinal cortical (area 28) input, but it is likely that area 23d receives a weak projection, since areas 24b′ and d23b have such input.

Cingulate projections to the entorhinal cortex have been demonstrated using retrograde tracing methods (Insausti *et al.* 1987). Entorhinal cortex receives input from cingulate cortex, extending from anterior to posterior levels, that is, areas 24, 25, 32, 23, 29l, 30. Although Insausti *et al.* (1987) used the nomenclature of Pandya *et al.* (1981) and Vogt (1985), their delineations of these areas were very different and have changed over the years. When the sites of origin in the cingulate cortex were described on the basis of Vogt *et al.* (2005) subdivisions, it can be seen that areas 24, a24a′/b′, p24a′/b′, 25, 32, 23d, d23a/b, v23a/b, and 30 are delineated. There appears to be no projection from regions within the cingulate sulcus to the entorhinal cortex (Morecraft and Van Hoesen, 1998). Further, the main recipient regions in the entorhinal cortex was its caudal part (Insausti *et al.* 1987).

The neurons of origin in the cingulate cortex are located almost exclusively in layer III. Anterograde tracing studies demonstrated that areas 24 and 32 project to the entorhinal cortex; laminar distribution of the terminals and fibers was not described (Pandya *et al.*, 1981; Chiba *et al.*, 2001). Using the sensitive anterograde tracer BDA, our own studies show that injections into area 24 and v23 label terminals in layers I-III and V of entorhinal cortex (unpublished data).

Perirhinal Cortex

An early HRP study (Baleydier and Mauguire, 1980) reported that the PCC, including RSC, receives input from the perirhinal cortex, while ACC area 24 does not. Although subsequent studies failed to demonstrate labeled cells in perirhinal cortex following ACC or PCC HRP injections (Vogt and Pandya, 1987; Bachevalier *et al.*, 1997), several more recent retrograde tracing studies showed that ACC areas 24 and 32 received projections from perirhinal cortex areas 35 and 36 (Arikuni *et al.*, 1994; Muñoz and Insausti, 2005). Recent studies also have shown that there is a substantial projection from the perirhinal cortex to area 30 or 29/30 (Morris *et al.*, 1999; Yukie *et al.*, 2002; Kobayashi and Amaral, 2003). Further, Morecraft *et al.* (2004) reported that area 23c in the cingulate sulcus receives input from perirhinal area 35. In addition, our recent retrograde tracing study has demonstrated that areas d23b and v23b also receive input from layer V of perirhinal areas 35 and 36 (Yukie *et al.*, 2002). One anterograde tracing study with tritiated-amino-acid and WGA-HRP injections in the perirhinal cortex demonstrates that perirhinal cortex projects to a region corresponding to areas 24 and 24′ but not to areas 25, 32 or the PCC (Lavenex *et al.*, 2002) and does not confirm the findings from retrograde tracing studies. Thus, overall, perirhinal cortex
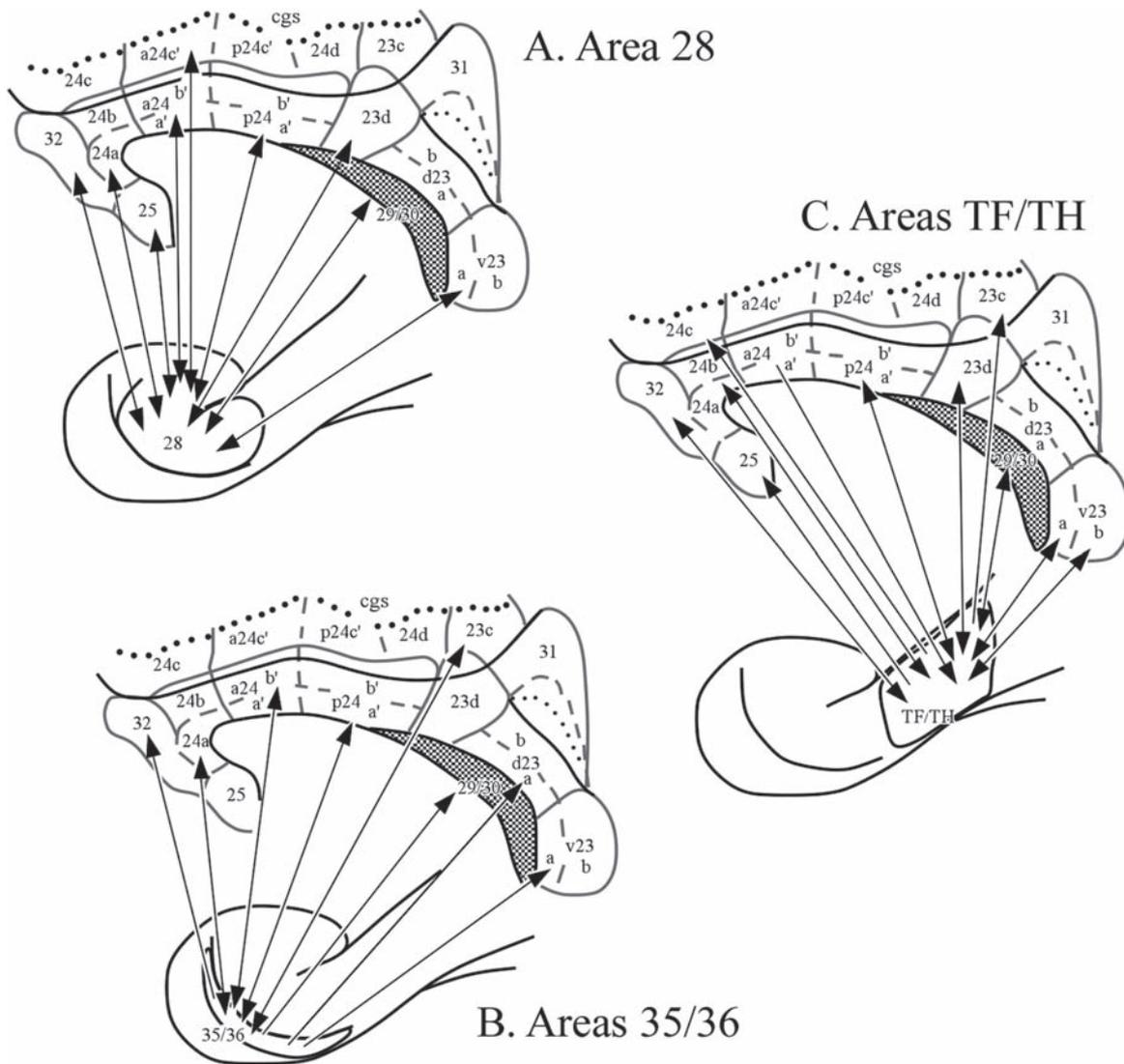
Fig. 6.3 Diagrams of parahippocampal and perirhinal connections with the cingulate gyrus. A. Entorhinal-area 28- connections, B. Perirhinal - area 35/36- connections, and C. Posterior parahippocampal areas TF and TH connections.

projects to the cingulate cortex and these projections are very weak.

Regarding projections from the cingulate cortex to perirhinal cortex, there is some discrepancy between anterograde and retrograde tracing studies. One anterograde tracing study showed that the caudal part of area 24 (maybe area 24´) projected to the perirhinal cortex, while areas 24, 32, 23, and 29/30 did not (Pandya et al., 1981). Other studies using retrograde fluorescent tracer injections into perirhinal area 36 produced a small number of labeled neurons in areas 24, 25, and 32, including area 24´ of Vogt et al. (2005) classification, but not in PCC or RSC (Suzuki and Amaral,1994; Chiba et al., 2001; Blatt et al., 2003). Thus, perirhinal cortex

projects to the ACC (area 24), MCC (area 24´), PCC (areas d23b, v23b, and 23c), and RSC (area 30), and it receives projections from the MCC (area 24´) and ACC (areas 24, 25, and 32) but not from the PCC or RSC.

Posterior Parahippocampal Cortex

Areas TF and TH occupy major parts of the posterior parahippocampal cortex, and it is clear that cingulate cortex receives input from these two areas (Baleydier and Mauguiere, 1980; Van Hoesen, 1982; Vogt and Pandya, 1987). Earlier studies showed that the PCC (area 23) receives strong input from TF and TH, while the ACC (area 24) does not receive so strong an input (Vogt et al., 1979; Baleydier and Mauguiere, 1980).

More recent studies employing retrograde and antero-grade tracing methods showed that most of the cingulate areas, including the areas within the cingulate sulcus, receive input from areas TF and TH (Vogt and Pandya, 1987; Van Hoesen *et al.*, 1993; Morecraft and Van Hoesen, 1998; Bachevalier *et al.*, 1997; Morris *et al.*, 1999; Lavenex *et al.*, 2002; Kobayashi and Amaral, 2003; Morecraft *et al.*, 2004). ACC area 24 including areas 24c, 25, and 32, receive input from areas TF and TH (above studies). Although there has not yet been direct evidence showing a projection to the MCC, HRP experiments with injec-tions in the MCC that involved caudal area 24 and rostral area 23 demonstrated retrograde labeling in area TF. Projections to area 24 arose mainly from layer V of areas TF and TH (Vogt and Pandya, 1987; Arikuni *et al.*, 1994). Projections from the parahippocampal cortex terminated in layers I-III of the cingulate cortex (Lavenex *et al.*, 2002). The PCC including areas d23, v23, 23c, and 31, receives projections from areas TF and TH (Vogt and Pandya, 1987; Morecraft and Van Hoesen, 1998; Lavenex *et al.*, 2002; Morecraft *et al.*, 2004). Interestingly, projections to the PCC originate from layers III and V of area TF (Yukie *et al.*, 2002; Kobayashi and Amaral, 2003).

Regarding the projections to the RSC, area 30 receives input from area TF (Morris *et al.*, 1999; Kobayashi and Amaral, 2003). How strong the input to area 29 from area TF is unclear, since it is difficult to produce a case with an injection restricted to area 29. However, since anterograde injections into TF failed to produce labeling in area 29 of Vogt's (2005) classification (Lavenex *et al.*, 2002), area 29 may not receive a projection, or only a very weak one.

Projections from cingulate cortex to areas TF and TH were seen after large injections of tritiated amino acids into areas 24 and 23; the injections also included areas 29 and 30 (Baleydier and Mauguiere, 1980; Pandya *et al.*, 1981). Retrograde tracer injections into area TF also demonstrated that areas 23 and 24, including 23v and 23d, project to TF and that area 29/30 does not (Lavenex *et al.*, 2002). Another study that placed isotope injec-tions into area 30 indicates that it projects to areas TF and TH (Morris *et al.*, 1999). However, this finding needs to be corroborated, since the isotope injection appeared to also include area 23, a subdivision that by itself projects to TF and TH. Isotope injections into the MCC, which might have included areas 24′ and 23d, produced labeled terminals in area TF in and around the rostral occipitotemporal sulcus. It is unlikely that areas 32 or 25 of ACC project to area TF or TH (Pandya *et al.*, 1981; Lavenex *et al.*, 2002).

Temporal Pole Projections

The temporal pole is located at the most rostral tip of the temporal lobe and comprises area TG in the mon-key (von Bonin and Bailey, 1947). Cytoarchitectonically, area TG contains agranular, dysgranular, and granular subareas (Morán *et al.*, 1987; Carmichael and Price, 1995; Kondo *et al.*, 2003). Many studies show that area TG is connected reciprocally with the ACC (Markowitsch *et al.*, 1985; Vogt and Pandya, 1987; Morán *et al.*, 1987; Kondo *et al.*, 2003), but not with the PCC (Vogt and Pandya, 1987; Vogt, 1993).

Kondo *et al.* (2003) examined orbital and medial pre-frontal connections, including the ACC, by placing small injections of retrograde and anterograde tracers into subdivisions of area TG. The dorsal part of area TG (area TGdg of Kondo *et al.*, 2003) connects with areas 24, 25, and 32 of the ACC. They indicated that reciprocal and strong connections exist between the dorsal part of TG and areas 25 and 32. TG connections, however, are very weak with area 24, a finding also reported by Morán *et al.* (1987). Another study that placed large HRP injec-tions into area 24, however, indicated that area 24, rather than area 25, receives afferents from area TG (Van Hoesen *et al.*, 1993). Chiba *et al.* (2001) demonstrat-ed that BDA injections into area 24a/b produced labeled terminals in TGa, a segment of TG delineated by Kondo *et al.* (2003). Morecraft and Van Hoesen (1998) demon-strated that area 24c of the anterior cingulate sulcus receives input from area TPdg.

Superior Temporal Gyrus Projections

The superior temporal gyrus (STG) comprises primary and association auditory cortical areas. Van Hoesen *et al.* (1993) described cingulate cortex afferent projec-tions from areas Pro (roughly corresponding to area TG), Ts1, Ts2, Ts3 (Pandya and Sanides, 1973), and TPO (Selzer and Pandya, 1978) of the dorsal bank of the superior temporal sulcus (sts). Different rostrocaudal levels of the cingulate cortex receive projections from different areas of the STG. Retrograde injections into the most rostral and ventral parts of area 25 labeled cells in area Ts2 and the ventral part of area Ts3 of the STG; injections into rostral area 24 labeled cells in area Pro and the caudal part of area Ts1; injections into the MCC, including area 24′ and rostral part of area 23, labeled cells in the caudal part of Ts3; and finally, injections into the PCC, includ-ing areas 23, 30, and 29, labeled cells throughout the rostrocaudal extent of area TPO. Thus, auditory input to the PCC originates from area TPO.

Yukie (1995) examined connections of the PCC and RSC after WGA-HRP injections into the rostral, middle, and caudal regions of superior temporal cortex (area TA of von Bonin and Bailey, 1947). The injection sites cor-responded roughly to area Ts2, rostral Ts3, and areas paAlt and Tpt. Labeled cells and terminals were observed in area d23a/b with an ordered density gradient corre-sponding to the injection site location: progressively more caudal injections resulted in progressively heavier

labeling of cells and terminals in area d23a/b. Further, injections into middle and rostral regions labeled cells and terminals in area v23a/b, and not in area 29/30 within the caudomedial lobule (CML; Goldman-Rakic *et al.*, 1984), an area previously shown to have connections with auditory association cortex. Area v23 was connected more strongly with the middle region than the rostral region, and the rostral and middle regions were connected more strongly with area v23 than with area d23. The rostral (Ts1 and Ts2) and middle (Ts3) regions possess reciprocal connections with areas 24, 25, and 32 of ACC (Müller-Preuss *et al.*, 1980; Petrides and Pandya, 1988; Vogt and Barbas, 1988; Van Hoesen *et al.*, 1993). These connections are summarized in Figure 6.4.
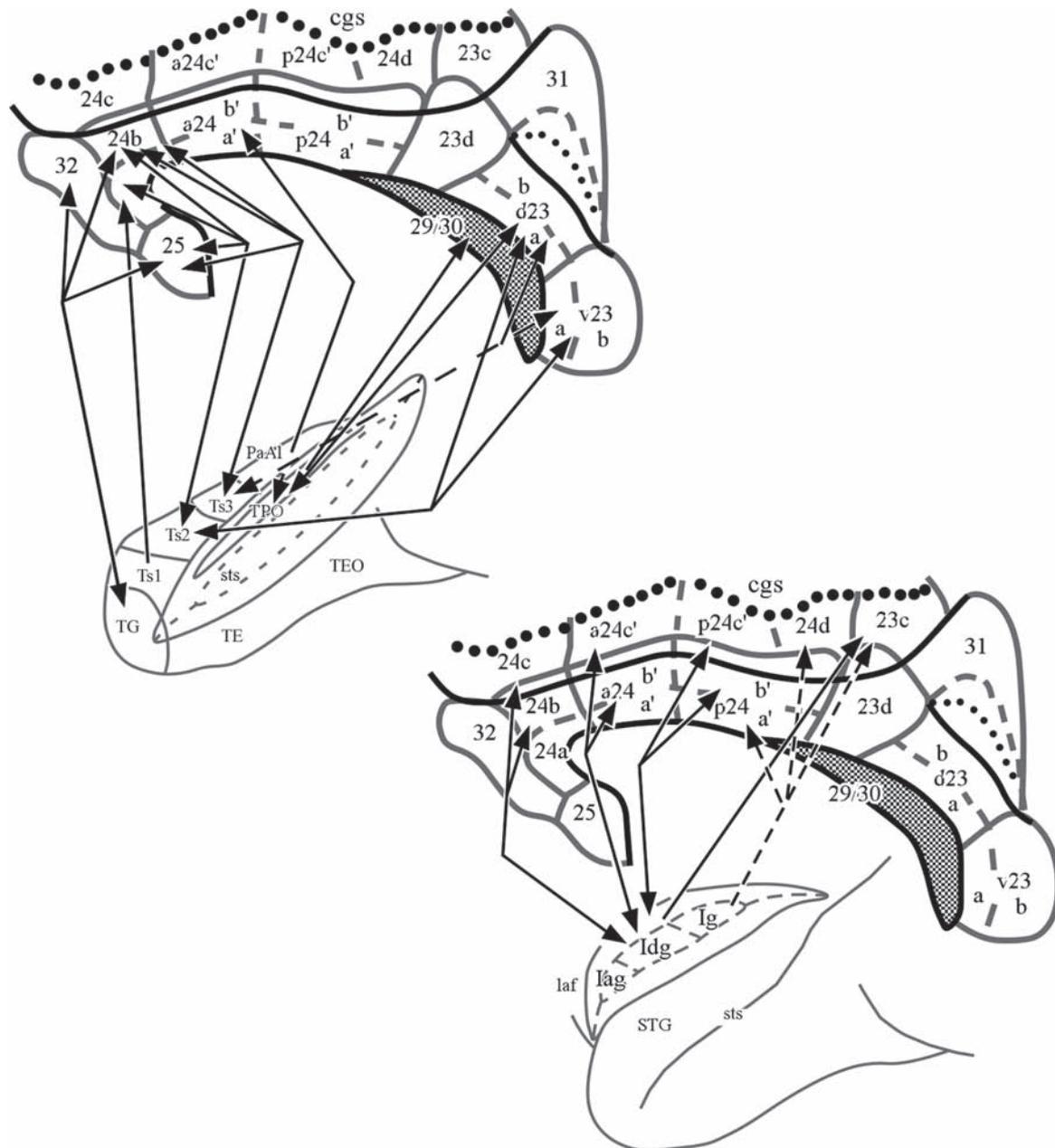

Fig. 6.4 Temporopolar and superior temporal connections with the cingulate cortex (Top) and the insula (Bottom). The superior temporal sulcus (sts) and lateral fissure (laf) have been opened in this view (lower lighter diagrams) and marked with dashed lines. Related cytoarchitectual divisions of cingulate and superior temporal cortices and the insula are outlined by thin gray lines. Abbreviations: Ia-p, agranular- periallocortical area of insula; Idg, dysgranular area of insula; Ig, granular area of insula.

Recently, a retrograde tracing study of connections to areas 29/30 of the CML showed that it receives a minor input from the STG and the dorsal bank of the sts, while area 23 receives substantial input from the caudal part of STG and dorsal bank of the sts containing areas Tpt and TPO (Kobayashi and Amaral, 2003). The same study also showed that area 23 receives substantial input from the caudal part of the STG and the dorsal bank of the sts containing areas Tpt and TPO. Their injection in areas 29/30 of the CML probably avoided area v23, since it failed to produce substantial neuron labeling in the STG (Yukie, 1995).

Area 24′ might connect reciprocally with area TPO within the sts, since HRP and isotope injections that include the MCC produce labeled cells and terminals in area 24′ (Pandya *et al.*, 1981; Van Hoesen *et al.*, 1993). However, further study is necessary since there is no study demonstrating the connections of individual areas within the MCC.

Efferents from the cingulate gyrus have been demonstrated by HRP injections into the STG and sts (Baleydier and Mauguire, 1980) and by anterograde tracer injections into the cingulate cortex (Müller-Preuss *et al.*, 1980; Pandya *et al.*, 1981; Vogt and Pandya, 1987). HRP injections in temporal area 22 or into the dorsal bank of the anterior sts labeled cells only in the PCC (Baleydier and Mauguire, 1980). Pandya *et al.* (1981) used tritiated amino acid injections to show that area 23 of PCC sends efferent projections to sts area TPO, while area 32 of the ACC projects to the lower middle STG, corresponding to area Ts2 and Ts3. However, the caudal part of area 24 and 24′ did not provide a substantial projection to the STG. Seltzer and Pandya (1994) systematically examined the projections to the sts, especially of area TPO, from the cingulate cortex and concluded that mid and caudal TPO (TPO-2, -3, -4) received projections from areas 23, 24, and RSC, although rostral sts area TPO-1 did not receive projections from the cingulate cortex.

Insular Connections

The insula is composed of cortex within the lateral fissure and is covered by frontal, parietal, and temporal opercula. A diagram of the interconnections between the insula and cingulate gyrus is presented in Figure 6.4. The cytoarchitectonic structures of the insula and surrounding regions have also been reported (Mesulam and Mufson, 1982a, 1985). The insula contains several types of cortex that are arranged along a gradient of increasingly more granular layer IV. Three "belts" can be distinguished: (1) the most rostral is termed the agranular area Iag, because it lacks layer IV granule cells; (2) the intermediate dysgranular region is composed of area Idg, in which the granule cells in layers IV and II do not display complete laminar differentiation;

and (3) the caudal granular area Ig, which is essentially an isocortical structure with well-differentiated layers II and IV.

HRP studies showed that ACC or MCC areas 24, 32, and 24′, and the cingulate sulcus receive input from the insula (Mesulam and Mufson, 1982b; Vogt and Pandya, 1987), whereas areas 25, PCC and the RSC have no input from the insula (Vogt and Pandya, 1987). The latter negative findings have also been obtained by other retrograde tracing studies (Baleydier and Mauguire, 1980; Morris *et al.*, 1999; Kobayashi and Amaral, 2003). It seems unlikely that there are projections from the insula to areas 29, 30, d23, v23, 23d, or 25.

Anterograde experiments with injections of tritiated amino acids in the insula demonstrated labeling only in and around the cingulate sulcus through the anterior and posterior cingulate gyrus (Mesulam and Mufson, 1982b), which corresponds roughly to areas 23c, 24d, 24c′, and 24c. Indeed, injections of retrograde tracers into areas 24c and 23c showed that they receive inputs from areas Ig and Idg (Morecraft and Van Hoesen, 1998).

For projections from cingulate cortex to the insula, tritiated amino acid injections into the ACC showed mainly anterograde label in area Idg of the mid-insula, while injections into the MCC labeled cells in areas Ig and Idg of the mid-insula (Pandya *et al.*, 1981; Mufson and Mesulam, 1982). In the isotope experiment of Mufson and Mesulam (1982), labeled terminals were observed in all layers of the insula. Their HRP experiments demonstrated that posterior insula areas Ig and Idg received input from cortex in the cingulate sulcus throughout its anteroposterior extent, but not the gyral cortex. Anterior and mid-insula area Idg receive input from the ACC on the gyrus and in the sulcus but not from the posterior cingulate gyral or sulcal cortex. Other studies with isotope and BDA injections failed to show projections to the insula from anterior areas 32, 25, or posterior areas 23d, d23a/b, and v23a/b, including area 29/30 (Pandya *et al.*, 1981; Morris *et al.*, 1999; Chiba *et al.*, 2001).

Medial Temporal Interactions with the PCC and RSC

Although medial temporal lobe projections to the entire cingulate gyrus were considered above, those with the PCC and RSC are quite detailed and need to be considered separately and in terms of their functional implications. The medial temporal cortex receives direct or indirect input from five sensory modalities. The pathways from visual and auditory sensory cortex to the medial temporal areas are shown in Figure 6.5. Briefly, auditory information is sent from several auditory association areas (areas RP and Ts1/Ts2) to parahippocampal areas, TF2 and TH (Pandya and Yeterian,
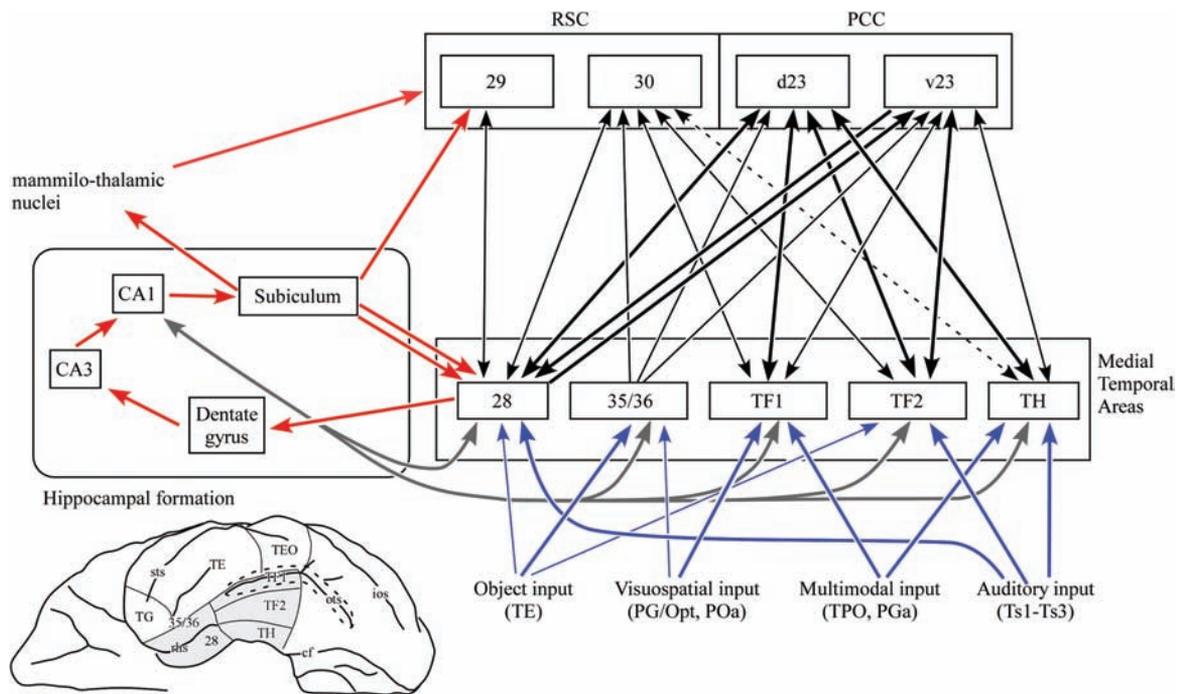
Fig. 6.5 Summary of medial temporal interactions with the RSC and PCC that suggest sources of sensory inputs (visual object, visuospatial, multimodal, auditory) and relationship between hippocampal formation information processing (red arrows in separate box on left) and the RSC via area 29.

1985; Suzuki and Amaral, 1994; Blatt *et al.*, 2003) and to entorhinal area 28 (Amaral *et al.*, 1983; Insausti *et al.*, 1987; Suzuki and Amaral, 1994). Although area TH projects to area Tpt of the caudal auditory association cortex (Tranel *et al.*, 1988), the reverse projection appears unlikely, since retrograde tracer injections into area TH failed to produce labeled cells in area Tpt (Blatt *et al.*, 2003).

Regarding visual information, the ventral visual pathway for object vision links area TE to perirhinal areas 35 and 36, entorhinal area 28, and parahippocampal area TF2 (Pandya and Yeterian, 1985; Suzuki and Amaral, 1994; Saleem and Tanaka, 1996; Blatt *et al.*, 2003), while the dorsal visual pathway for spatial vision links areas PG/Opt and LIP to areas TF1 in and around the occipito-temporal sulcus, the presubiculum of the parahippocampal cortex, and area 36 of the perirhinal cortex (Pandya and Yeterian, 1985; Martin-Elkins and Horel, 1992; Suzuki and Amaral, 1994; Ding *et al.*, 2000; Blatt *et al.*, 2003). Area TF1 also receives input from areas V3A, V4, and MST (Martin-Elkins and Horel, 1992; Blatt *et al.*, 2003).

Area TF2 also receives somatosensory input from the insula (Blatt *et al.*, 2003). TF1 and TH receive input from multimodal areas TPO and PGa (Blatt *et al.*, 2003). Areas 35 and 36, TF1, TF2, and TH have reciprocal

connections with one another (Suzuki and Amaral, 1994; Blatt *et al.*, 2003). Physiological studies (Blatt *et al.*, 2003) have demonstrated that areas TF1 and TF2 contain neurons responsive to visual stimulation, while area TH has neurons responsive to auditory stimulation. There are also some visually responsive units and bimodal units (auditory and visual) in area TH (Blatt *et al.*, 2003).

Among the medial temporal areas, the most substantial projection to the PCC and RSC originates in the posterior parahippocampal gyrus. Since these and other temporal projections have been considered in detail above, the following is a summary aimed to enhance overall understanding of the circuitry. It is well known that the PCC receives input from areas TF and TH. The PCC, including area d23/23d and v23, receive a substantial input from parahippocampal areas TF and TH. Areas 23c and 31 of the PCC and area 30 receive only weak projections from areas TF and TH. Finally, area 29 does not receive a projection from TF or TH. It is interesting that the dorsal part of area 30 receives projections from TF1, TF2, and TH, while the posteroventral part of area 30 receives projections almost exclusively from areas TH or TF2 but not TF1. Projections from cingulate cortex to areas TF and TH are well established and are known to include areas 23 and 29/30. Area TF1 receives

a projection from areas d23 and 30, and v23 projects mainly to areas TF2 but not to area TF1 in the occipito-temporal sulcus.

The parahippocampal and perirhinal cortices send information via the entorhinal cortex to the dentate gyrus of the hippocampal formation which, in turn, projects to the CA3 field and from there, to the field CA1 of the hippocampus. Field CA1 sends fibers to the subiculum and projects back to extensive cortical regions including the parahippocampal and perirhinal cortex, the ventral inferotemporal cortex, anterior sts, and the orbitomedial prefrontal cortex. CA1 also receives direct inputs from widespread areas of temporoparietal cortex, as noted in the above cited articles and as summarized in Figure 6.5.

The subiculum projects to the mammillary bodies, entorhinal cortex, and surrounding cortices. At the same time the subiculum projects to retrosplenial area 29 but not to PCC. In contrast, the projections from the anterior nuclei of the thalamus are directed to both the PCC and RSC, which are described in Chapter 4 and by Shibata and Yukie (2003). There is no projection from area 29 to the subiculum, and the dorsal and posteroventral parts of areas 30 and 29 receive inputs from the presubiculum. The presubiculum receives input from different association cortices, such as the inferior parietal cortex, rostral auditory association cortex (Ts1/2), and inferotemporal cortex.

In summary, the principal afferents from the medial temporal lobe to the PCC and RSC originate in the posterior parahippocampal cortex (areas TF and TH), and the subiculum, while minor afferents originate in entorhinal area 28 and perirhinal areas 35/36. The major efferents from the PCC and RSC to the medial temporal lobe are directed to entorhinal area 28 and parahippocampal areas TF and TH, but only sparsely to the perirhinal cortex. Areas d23 and v23 of PCC and areas 29 and 30 of the RSC project substantially to the entorhinal cortex and to the parahippocampal cortex, TF and TH.

Auditory Information Flow within the Temporal Lobe and to Cingulate Cortex

The anatomy and connections of auditory-related cortices of the monkey have been explored in many previous studies (Pandya *et al.*, 1969; Jones and Powell, 1970; Merzonich and Brugge, 1973; Fitzpatrick and Imig, 1980; Galaburda and Pandya, 1983; Morán *et al.*, 1987; Morel *et al.*, 1993; Cipolloni and Pandya, 1989). Recently, chemoarchitectonic studies have made it possible to delineate the auditory core, belt, and parabelt regions (Jones *et al.*, 1995; Hackett *et al.*, 1998). The flow

of auditory information is reflected anatomically as functionally organized regions within the subdivisions of Hackett *et al.* (1998) with complementary areas of Galaburda and Pandya (1983); the latter subdivisions were also studied by single-unit mapping (Rauschecker *et al.*, 1995, 1997).

Figure 6.6 shows the area delineations and auditory information flow in the monkey. One of the major streams from primary auditory cortex (AI) is the ventral pathway via the rostral area (R) and anterolateral area (AL) to the rostral parabelt region (PR). Another one is the dorsal pathway via the mediolateral area (ML), caudomedial area (CM), and caudolateral area (CL) to the caudal parabelt region (CP), including area Tpt. An interesting recent proposal is that the ventral and dorsal streams might be involved in cortical processing of auditory pattern and spatial information, respectively (Rauschecker and Tian, 2000; Tian *et al.*, 2001). Physiological studies have found that the CM, CL, and Tpt adjacent to or overlapping with the CM and CL, contain abundant spatially tuned neurons to auditory stimulation (Leinonen *et al.*, 1980; Rauschecker and Tian, 2000; Tian *et al.*, 2001), while AL contains a number of neurons selectively responsive to monkey calls and complex sounds (Rauschecker and Tian, 2000; Tian *et al.*, 2001). Further, Lewis and Van Essen (2000) have suggested that area Tpt and their area Toc (which may overlap with area CL) have light projections to some parts of the intraparietal sulcus (area VIP, see below) of the parietal cortex.

Earlier anatomical studies showed that the auditory association cortex projects to both the ACC and PCC including the RSC. The PCC, including areas d23, 30, and 29, receives afferents from area TPO in the sts (Vogt and Pandya, 1987) but not from the supratemporal plane or STG. This finding suggests that auditory input to the PCC and/or RSC is provided through area TPO, which is a multimodal sensory area receiving input from auditory association cortex and visual association cortex (Seltzer and Pandya, 1994). This study, however, did not examine whether the RSC and the CML receives auditory input. The CML forms a promontory-like structure, and the cortex bends caudally around the corpus callosum. Damage to this lobule produces so-called "retrosplenial amnesia" (Valenstein *et al.*, 1987). According to the view in Chapter 3, area v23b forms the CML, while areas 29 and 30 lie lateral to this structure in the callosal sulcus (Vogt *et al.*, 2005).

As already described, Yukie (1995) examined connections of the PCC and RSC by making WGA-HRP injections into the rostral, middle, and caudal regions of superior temporal area TA (von Bonin and Bailey, 1947) in an effort to understand the flow of auditory information into this region. The injection sites corresponded roughly to area Ts1/Ts2, RP, and CP including
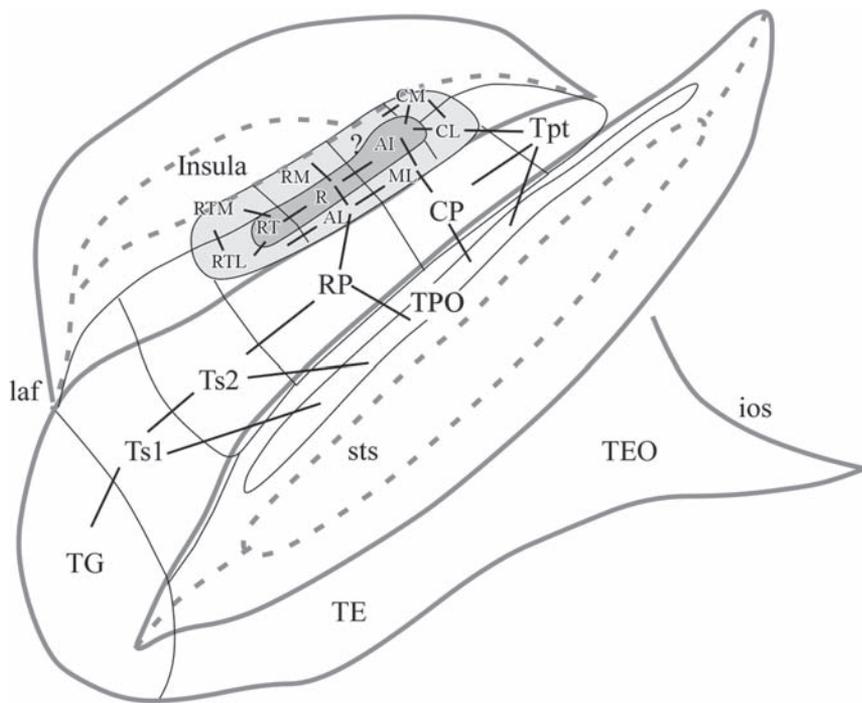
Fig. 6.6 Organization of the auditory cortex and aspects of auditory information flow. TG is the temporal pole area; the auditory areas are in the lateral fissure (laf) on the superior temporal plane, and the sts has been opened up, exposing the insula (demarcated with dashed lines). Although the cingulate cortex does not have direct connections with primary and association auditory cortices, it has extensive and reciprocal connections with association areas in the STG and area TPO in the sts.

area Tpt, respectively. To summarize, area Tpt/CP projects to area d23 but not to area v23, while areas Ts1/Ts2 and RP project to area v23 with minor projections to area d23. These auditory association areas do not send fibers to the RSC, area 29 or 30. Since area TPO receives projections from the CML (Seltzer and Pandya, 1994), there is a possibility that the CML receives input from area TPO. Thus, it is likely together with the results of Vogt and Pandya (1987) that areas d23 and v23 receive auditory-related multimodal input from area TPO.

Tracer injections into area 29 and/or area 30 were attempted in two studies in monkeys to clarify the cortical connections of the RSC. According to Morris *et al.* (1999), area 30 receives afferents from areas TPO, Ts1, and TAa. In addition, a case with injections into dorsal area 30 showed afferents from area Tpt. Kobayashi and Amaral (2003) showed that retrograde fluorescent dye injections into areas 29/30 and parts of area 23 labeled a substantial number of cells in the caudal part of the STG (roughly corresponding to area CP/Tpt) and in the dorsal bank of the sts, which contains area TPO. Area 29/30 received a minor input from the STG or the dorsal bank of the sts.

Thus, auditory input to the posterior cingulate region is directed to area 23, and less so to retrosplenial areas 29 and 30. In the PCC, area d23 and area v23 have different patterns of projection origins. Area d23 receives input from the caudal part of the STG, including

area CP/Tpt, while area v23 receives input from the mid and rostral parts of the STG, including areas RP, Ts3, and Ts2/Ts1. Therefore, it is likely that areas d23 and v23 might have distinct functional significance in auditory-related processing, that is, area d23 might be related to auditory spatial processing, while area v23, might be related to auditory pattern processing. Further, the RSC also might have a different role from the PCC, since the RSC has much less input from auditory association cortex.

The Posterior Cingulate Duality: Areas d23 and v23

The PCC is not uniform on many levels of analysis. Shibata and Yukie (2003) showed that area d23 has unique inputs from the mediodorsal, central latocellular, and ventral anterior and lateral nuclei. In terms of cytology, Vogt *et al.* (2005) showed in the monkey that areas d23 and v23 differ and they subsequently showed in human a similar structural organization and proposed the possibility of differential circuitry using measures of resting glucose metabolism (Chapter 13). In view of this striking structural and functional dichotomy in PCC, it is important that cortical connections be evaluated in a similar context.

Area d23 receives projections from the auditory association cortex, especially from its caudal areas, CP and Tpt, which are considered to mediate auditory
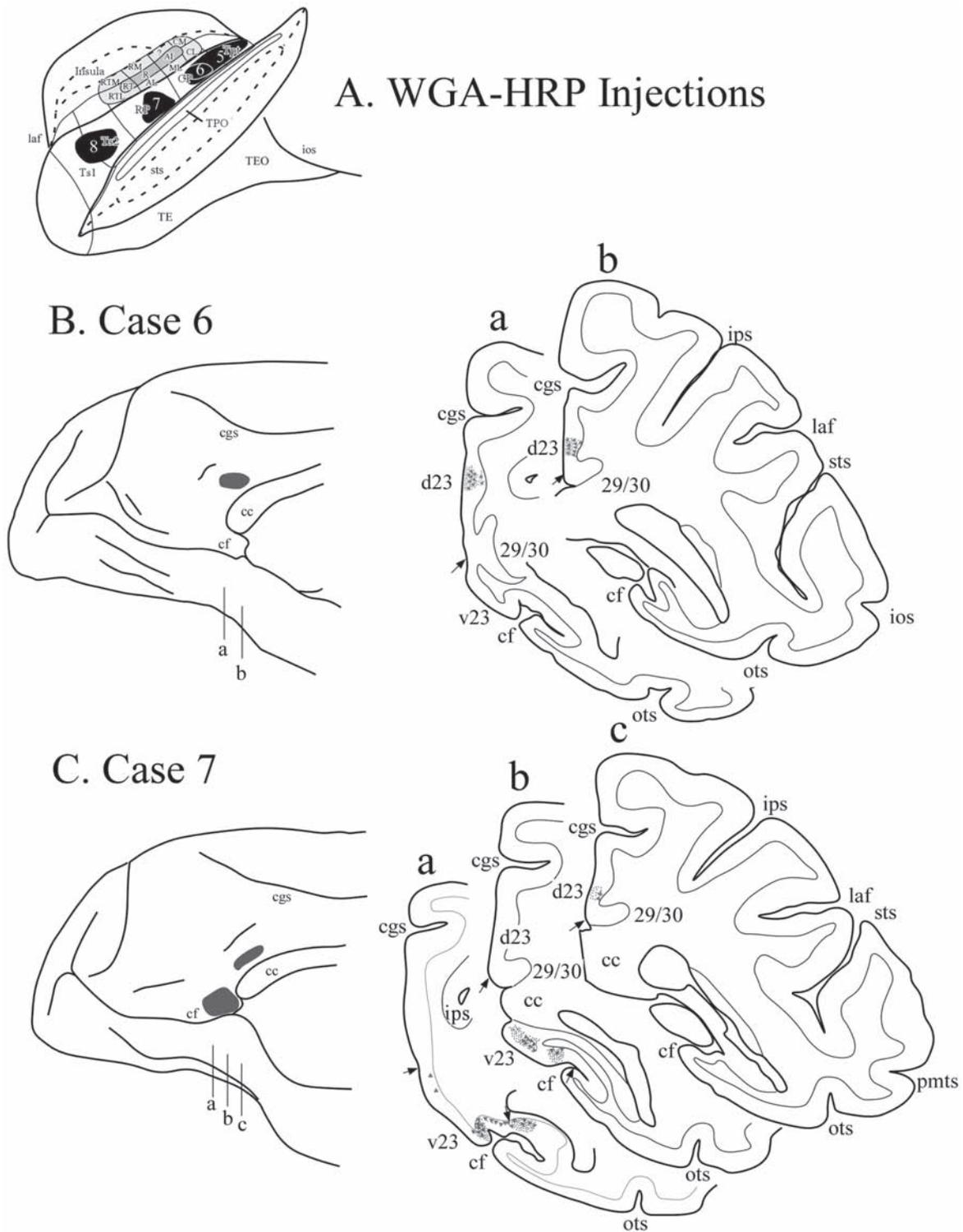
Fig. 6.7 A. WGA-HRP injections (black areas) in the STG areas likely involved in auditory processing. The lateral fissure (laf) and superior temporal sulcus (sts) are opened up in the upper left diagram for orientation. Distribution of dye labeling in two cases with CP (B.) and RP (C.) injections. Labeled sites in the PCC are indicated by gray zone in the medial surface of brain. The large and small dots are associated, respectively, with retrograde and anterograde labeling from injections mapped in A. The figure was redrawn from Yukie (1995). Temporocingulate Interactions in the Monkey.

spatial processing. Thus, area d23 might be related to auditory spatial processing, although there has been no supportive evidence in functional studies. On the other hand, in area LIP of the monkey parietal cortex, physiological studies have demonstrated that there are neurons with spatially tuned auditory responses. Almost all of them are bimodal and spatially tuned in their visual responses (Mazzoni *et al.*, 1996). Further, there are many LIP cells active during the memory period in a memory saccade task for briefly presented auditory targets in the dark (see Andersen, 1995; Stricanne *et al.*, 1996). Possibly, the LIP zone containing such responsive neurons receives auditory input from the caudal part of STG, since there is an anatomical study showing such a connection (Lewis and Van Essen, 2000). Since area d23, as well as 23c, 23d, 31, and 29/30 have reciprocal connections with area LIP as described above, such activity of LIP neurons could be transmitted to dorsal parts of the PCC and RSC. Area d23 also receives input from PG/Opt, LOP, MST, and DP.

"Retrosplenial amnesia" was first considered to be caused by damage to the RSC and adjacent PCC, including area v23 in the CML (Valenstein *et al.*, 1987). Cortical connections of the RSC are mainly characterized by subicular input to area 29. This projection contains information processed in the hippocampus, which receives auditory and visual information that is transmitted via the parahippocampal, perirhinal, and entorhinal cortices, as summarized above. The auditory, spatial, and memory inputs to the posterior cingulate gyrus respect, in many ways, the PCC duality.

First, auditory input is different among these areas; area d23 receives input mainly from areas Tpt and CP of the caudal auditory association cortex, while v23 receives input exclusively from area RP and Ts1/Ts2; area 29 or 30 of RSC receives less direct input from these auditory association areas. As described, this considerable discrete differentiation of auditory flow to areas d23 and v23 suggests that there might be some functional difference in auditory-related processing between areas d23 and v23 and that d23 might contribute to auditory spatial orientation, while v23 might be involved in auditory pattern (verbal) memory. The caudal auditory association cortex (areas Tpt and CP) belongs to the auditory spatial processing system, while the rostral auditory association cortex belongs to auditory pattern processing system.

Second, parietal interactions with the PCC are also different between the dorsal and ventral portions. The dorsal portion, including areas d23 and 29/30 above the corpus callosum, has strong connections originating in areas Opt, LIP, and PGm, while the ventral portion, including areas v23 and 29/30, has only weak connections with areas LIP and Opt. According to Olson *et al.* (1993; 1996) posterior cingulate neurons, which occupy

area d23 but not v23, show postsaccadic activity that monitors eye movement and eye position (Olson *et al.*, 1993; 1996); this suggests that these areas participate in assigning coordinates to retinal images. This postsaccadic activity was significantly dependent on saccadic amplitude, that is, on larger saccades. Areas PG/Opt, PGm, and VIP receive projections from the dorsomedial "large-saccade" sector of the frontal eye fields (Stanton *et al.*, 1995). Therefore, postsaccadic activity in posterior cingulate neurons might depend on input from areas PG/Opt and PGm. It is unlikely that areas v23 and 29/30 contribute strongly to a similar functional role as that of area d23, since they have only weak connections with parietal cortex (Morris *et al.*, 1999; Kobayashi and Amaral, 2003). Instead, they likely contribute strongly to auditory pattern or auditory verbal memory, as described above.

Third, the interactions of the PCC and RSC with the medial temporal lobe are considered to constitute part of the memory system, since damage to components of the medial temporal cortex leads to some memory deficits. Area 29 is positioned in a special site within the PCC and RSC, since it alone receives a direct input from the subiculum. Since the subiculum provides hippocampal output to area 29, it might play a special role in memory function in the posterior cingulate region. However, it still remains unclear what concrete functional role this projection might have.

Another subicular influence to the PCC and RSC is provided via the mammillary bodies and the anterior thalamus. Since damage that includes the left and right anterior thalamus produces impairment, respectively, in auditory-verbal memory and visuospatial memory (Graff-Radford *et al.*, 1990; Clarke *et al.*, 1994; Ghika-Schmid and Bogousslavsky, 2000), the subiculo-mammillo-thalamic pathways might be a critical part of such memory systems. On the other hand, no one has gathered evidence about the functional roles of area 29 or 30 in primates by themselves, since no known patients exist with restricted lesions of area 29 or 30, and functional correlates of area 29 or 30 neurons are not yet demonstrated. To understand the functional significance of the RSC areas 29 and 30, it will be necessary to explore the physiological properties of neurons and their functional correlates.

Among the parahippocampal and perirhinal cortical areas, TF1, TF2, and TH provide strong output to areas d23, v23, and 30, while areas 28 and 35/36 have only a very weak output to these cingulate areas. Area TF1 receives input from area PG-Opt and LIP of the parietal cortex and projects to areas d23, 23d, and v23 and 30, with the predominance of projections terminating in the dorsal part of PCC. Area TF2 receives inputs from auditory area Ts1-3, including the RP, provides heavier projections to area v23 than to areas d23, 30, and 29.

Area TH receives inputs from auditory area Ts1-3, including RP, and sends outputs to area v23. Areas TF and TH contribute to auditory spatial and visuospatial memory, since area TF/TH receive input from auditory association cortex and inferior parietal cortex. Patients with lesions to the right parahippocampal cortex and the right hippocampus are impaired in visuospatial memory (Bohbot *et al.*, 1998).

Circuitry Overview

While the cingulate gyrus was originally believed to be a central component of a brain-circuit subserving emotion, it is now clear from more detailed anatomical analyses and functional studies in monkeys and humans that its robust connections with temporal and parietal cortices place it in a much broader network involved in higher cognitive function. Further anatomical and electrophysiological studies in the monkey and functional imaging studies in humans will precisely define its role in emotion, memory, and auditory information processing and most likely also reveal new roles.

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