Perirhinal and Parahippocampal Cortices of The Macaque Monkey: Projections to The Neocortex

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ABSTRACT

We investigated the topographic and laminar organization of the efferent cortical projections of the perirhinal and parahippocampal cortices. Area 36 of the perirhinal cortex projects preferentially to areas TE and TEO, whereas area TF of the parahippocampal cortex projects preferentially to the posterior parietal cortex and area V4. Area TF projects to many regions of the frontal lobe, whereas area 36 projects mainly to the orbital surface. The insular and cingulate cortices receive projections from areas 36 and TF, whereas only area TF projects to the retrosplenial cortex. Projections to the superior temporal gyrus, including the dorsal bank of the superior temporal sulcus, arise predominantly from area TF. Area 36 projects only to rostral levels of the superior temporal gyrus. Area TF has, in general, reciprocal connections with the neocortex, whereas area 36 has more asymmetric connections. Area 36, for example, projects to more restricted regions of the frontal cortex and superior temporal sulcus than it receives inputs from. In contrast, it projects to larger portions of areas TE and TEO than it receives inputs from. The efferent projections of areas 36 and TF are primarily directed to the superficial layers of the neocortex, a laminar organization consistent with connections of the feedback type. Projections to unimodal visual areas terminate in large expanses of the cortex, but predominantly in layer I. Projections to other sensory and polymodal areas, in contrast, terminate in a columnar manner predominantly in layers II and III. In all areas receiving heavy projections, the projections extend throughout most cortical layers, largely avoiding layer IV. We discuss these findings in relation to current theories of memory consolidation. J. Comp. Neurol. 447:394–420, 2002.

Indexing terms: hippocampal formation; topography; anterograde tracer; retrograde tracer; consolidation; memory

The description of the amnesic patient H.M. by Scoville and Milner (1957) firmly established the importance of the medial temporal lobe in memory function. Recent advances in characterizing human memory processes indicate that the brain supports multiple memory systems, which are subserved by different neural systems (Squire, 1992). Damage to the human medial temporal lobe results in a severe memory impairment characterized by rapid forgetting of declarative information but intact non-declarative memory (Squire and Zola-Morgan, 1996).

The development of animal models has been invaluable to our understanding of the function of the medial temporal lobe. The hippocampus was initially thought to be the primary substrate for declarative memory processes. But recent animal research using selective lesioning techniques and electrophysiological methods has emphasized that other regions, including the perirhinal and parahippocampal cortices, also contribute to normal memory function. Studies in monkeys and rats show that in certain tasks, lesions restricted to the perirhinal or the parahippocampal cortex produce severe memory deficits (Zola-
Morgan et al., 1989; Otto and Eichenbaum, 1992; Meunier et al., 1993; Mumby and Pinel, 1994) and can also exacerbate the deficit observed after lesions of the hippocampus (Zola-Morgan et al., 1993; Wiig and Bilkey, 1995).

We have previously demonstrated (Suzuki and Amaral, 1994a) that the perirhinal and parahippocampal cortices are the sites of convergence of unimodal and polymodal sensory information. The perirhinal and parahippocampal cortices receive distinct cortical afferent projections and appear to be preferentially involved in the processing of certain types of sensory information. The perirhinal cortex receives unimodal inputs, which arise mainly from the visual areas TE and rostral TEO (areas defined by Von Bonin and Bailey, 1947). The parahippocampal cortex, in contrast, receives stronger input from more caudal visual areas and from polymodal association areas (Suzuki and Amaral, 1994a). The perirhinal and parahippocampal cortices then project to the entorhinal cortex which, in turn, projects to the dentate gyrus and the hippocampus via the perforant path (Amaral et al., 1987). The perirhinal and parahippocampal cortices receive return projections from the entorhinal cortex that generally reciprocate the input pathways (Suzuki and Amaral, 1994b). The perirhinal and parahippocampal cortices also project back to the neocortex (Van Hoesen, 1982).

The existence of such reciprocal connections has been the basis for speculation concerning the involvement of the medial temporal lobe in memory consolidation (Teyler and DiScenna, 1986; Alvarez and Squire, 1994; McClelland et al., 1995). Patients with damage to the medial temporal lobe (Scoville and Milner, 1957; Zola-Morgan et al., 1986) have a selective impairment in the ability to form new, long-term declarative memories for facts and events, whereas their older declarative memories remain largely intact. Furthermore, temporally graded retrograde amnesia has been demonstrated in humans and animals after selective lesions of the medial temporal lobe (Scoville and Milner, 1957;Cho et al., 1995; Myhrer and Wangen, 1996). Taken together, these observations suggest that there is a gradual consolidation of memory. Declarative information that is initially dependent on the medial temporal lobe gradually becomes independent of it. Permanent memory storage is then presumed to be widely distributed within the neocortex. Because the perirhinal and parahippocampal cortices appear to have widespread interconnections with neocortical association areas (Van Hoesen, 1982), the neocortical targets of the cortical efferents of the perirhinal and parahippocampal cortices are considered to be prime candidates for the final repositories of long-term memories (Mishkin, 1982; Damasio, 1989; Squire, 1992; Miyashita, 1993).

All recent theories of memory consolidation (e.g., Teyler and DiScenna, 1986; Alvarez and Squire, 1994; McClelland et al., 1995) are based on the hypothesis that the efferent projections from the medial temporal lobe to the neocortex represent a critical link in the long-term storage process. However, relatively little is known about the specific organization of these efferent projections. The specific patterns of these projections have important implications for both computational models and theories of long-term memory consolidation. For example, it would be critical to know whether the inputs and outputs are strictly reciprocal or whether some cortical regions receive stronger projections from the medial temporal lobe than others.

As part of ongoing studies of the neuroanatomic organization of the monkey perirhinal and parahippocampal cortices, we have examined the topography and laminar organization of the efferent projections from the perirhinal and parahippocampal cortices to the neocortex. We have addressed three main issues. First, we determined the topography of the efferent projections from the perirhinal and parahippocampal cortices to the neocortex. Second, we examined the degree of reciprocity (at the area-to-area level) of the projections between the neocortex and the perirhinal and parahippocampal cortices. Third, we examined the laminar organization of the terminations of the perirhinal and parahippocampal efferent projections in the neocortex.

MATERIALS AND METHODS
Fifteen Macaca fascicularis monkeys of either sex, each weighing 3–5 kg at the time of surgery, were used in these studies. The 15 monkeys received one injection of [3H]-amino acid ([H]-AA) into the perirhinal or parahippocampal cortex. In three of these monkeys, an injection of a retrograde tracer (Fast Blue or Diamidino Yellow) was placed in close proximity to the [3H]-AA. In a fourth monkey, the retrograde tracer wheat germ agglutinin conjugated to horseradish peroxidase (WGA-HRP) was co-injected through the same pipette as the [3H]-AA.

Surgery
For experiments conducted before August 1990, animals were preanesthetized with ketamine hydrochloride (8 mg/kg i.m.) followed by Nembutal (25 mg/kg i.p.) and mounted in a Kopf stereotaxic apparatus. A venous catheter was placed and Nembutal was supplemented as necessary throughout surgery. For experiments conducted from 1991 to 1998, animals were preanesthetized with ketamine hydrochloride (8 mg/kg i.m.), intubated with a tracheal cannula, and mounted in a stereotaxic apparatus. The animals were then placed on a mechanical ventilator where a surgical level of anesthesia was maintained with isoflurane. Using sterile procedures, the skull was exposed and a small hole was made at a site appropriate for the injection as determined from the atlas of Szabo and Cowan (1984). In the one case with simultaneous injection of anterograde and retrograde tracers (M-15-98), a presurgical magnetic resonance imaging scan was performed to further define the surgical coordinates. In all cases, electrophysiological recordings were performed to determine more precisely the appropriate dorsoventral coordinate for placement of the injection. A tungsten microelectrode was lowered through the intended injection site and extracellular multi- and single-unit responses were recorded along its trajectory. All tracer substances were dispensed through glass micropipettes by using air pressure pulses (Amaral and Price, 1983). After injection of the tracer, the pipette was slowly withdrawn and the wound sutured. Analgesics (0.15 mg/kg of oxymorphone given three times daily for 2 days) were administered immediately postsurgically, and a prophylactic regimen of antibiotics (50 mg/kg of Clarofan, three times daily) was administered during the first 5 days of the survival period. These procedures were approved by the institutional animal care and use committee and conform to NIH guidelines.
Anterograde tracer studies

The $^{3}$H-AA injections consisted of a single injection of 50–100 nl of 1:1 mixture of $[^{3}]$H]leucine and $[^{3}]$H]proline (concentrated to 100 $\mu$Ci/ul). Animals survived for 14 days (only 3 days for M-15-98, see below), then were deeply anesthetized with Nembutal (50 mg/kg i.v.) and perfused transcardially with 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). The brains were post-fixed for 6 hours in the same fixative, then cryoprotected in 10% and 20% glycerol solutions in 0.1 M phosphate buffer (pH 7.4). The brains were rapidly frozen in isopentane (Rosen et al., 1986) and stored at $-70^\circ$C until sectioning. Sections were cut at 30 $\mu$m on a freezing, sliding microtome and processed according to the protocol of Cowan et al. (1972) for the autorigraphic demonstration of the anterogradely transported isotope. Sections were counterstained with thionin to allow the determination of the cytoarchitectonic boundaries of the different cortical areas.

Retrograde tracer injections

One of three retrogradely transported tracers, Fast Blue (FB), Diamidino Yellow (DY), or WGA-HRP, was injected in the perirhinal or parahippocampal cortex of four monkeys. In three of these monkeys, an injection of a retrograde tracer (DY or FB, Dr. Illing, GmbH and Co.) was placed close to the $^{3}$H-AA injection in the ipsilateral hemisphere. In a fourth monkey, the retrograde tracer WGA-HRP (Sigma, St. Louis, MO) was mixed with the $^{3}$H-AA solution (final concentration 1% WGA-HRP) and was administered simultaneously through the same pipette as the $^{3}$H-AA tracer, following the procedure previously described in Amaral and Insausti (1992). In the cases with the fluorescent retrograde tracers DY and FB, between 500 and 1,500 nl of a 2% DY solution or between 500 and 650 nl of a 5% FB solution was dispensed. Both the FB and DY solutions were dissolved in distilled water. Animals survived for approximately 14 days for the FB and DY cases, and for 3 days for the one case with the combined $^{3}$H-AA/WGA-HRP injection. Animals were deeply anesthetized and perfused as described above. For DY and FB analysis, two 1-in-8 series of sections were immediately mounted on slides and stored desiccated at $-20^\circ$C until they were analyzed. The adjacent 1-in-8 series of sections processed for autoradiography was stained with thionin to allow the determination of the cytoarchitectonic boundaries of the different cortical areas. A 1-in-8 series of sections throughout the brain was processed for the demonstration of WGA-HRP by using tetramethylbenzidine as the chromogen (Mesulam, 1976).

Analysis

For the $^{3}$H-AA injections, the distribution of anterogradely transported tracer in the neocortex was analyzed using darkfield optics. The position and density of labeled fibers and terminals were plotted for every section in a 1-in-16 series (spaced every 480 $\mu$m) or in a 1-in-15 series (spaced every 450 $\mu$m for cases DM-42 and DM-46).

For the cases with DY or FB retrograde tracer injections, the distribution of retrogradely labeled cells in the neocortex was analyzed with a Nikon Optiphot microscope linked to PC-based StereoInvestigator (Microbrightfield, Inc., Colchester, VT). The position of each retrogradely labeled cell was plotted for every section in a 1-in-16 series (i.e., spaced every 480 $\mu$m) throughout the entire brain.

The topographic organization of the efferent projections from the perirhinal and parahippocampal cortices to the neocortex was represented by plotting the distribution of anterogradely labeled fibers and terminals on two-dimensional unfolded maps of the neocortex. The intensity of labeling was estimated visually and coded in four different levels: 0, no labeling; 1, low labeling; 2, moderate labeling; and 3, heavy labeling. The boundaries of the major cortical areas were microscopically determined and marked onto the printed sections, and unfolded maps were reconstructed as previously described (Suzuki and Amaral, 1994a,c). Different shades of gray on these maps represent the density of anterogradely labeled fibers and terminals. Retrogradely labeled cells in the neocortex were also represented on identical unfolded maps, as described in Suzuki and Amaral (1994a).

For cases with both anterograde and retrograde tracer injections, we constructed composite maps plotting the distribution of anterograde and retrograde labeling to compare the reciprocity of the connections between the perirhinal and parahippocampal cortices and areas of the neocortex. Anterogradely labeled fibers and terminals and retrogradely labeled cells are also plotted on coronal sections from six representative rostrocaudal levels throughout the brain to illustrate the relationship between the unfolded maps and standard coronal sections.

For illustrations of the injection sites and the laminar organization of the fiber and terminal labeling in the neocortex, negatives of 35-mm photomicrographs taken on a Leica Leitz DMRD microscope were digitally scanned with a Polaroid SprintScan 35 Plus scanner and levels were adjusted in Photoshop 5.0.

We also computed an index of reciprocity to demonstrate the relative strength of the afferent versus efferent projections of the perirhinal and parahippocampal cortices in various neocortical areas. Reciprocity index $= ((A + D)/(A + R + 2D)) - ((R + D)/(A + R + 2D))$; where A is the number of cortical columns (769-$\mu$m-wide segments of cortex used for the reconstruction of unfolded maps, see Suzuki and Amaral, 1994a, c) with anterograde labeling, R is the number of columns with retrograde labeling, and D is the number of columns with both anterograde and retrograde labeling. We should point out that this use of the term column relates to a convenient sampling unit rather than a functional unit of the cortex. This index was computed only for cortical areas that had a minimum of 10 columns of cortex that contained labeling (either anterograde or retrograde). The value of the index can vary from $-1$: only retrograde labeling; to $+1$: only anterograde labeling. An index value of 0 indicates an equal number of columns containing anterograde labeling and columns containing retrograde labeling in the same cortical area, i.e., highly reciprocal connections (at the area-to-area level).
The nomenclature and boundaries of the different cortical areas analyzed in this study are similar to those used previously (Suzuki and Amaral, 1994a). Thus we will only briefly summarize the subdivisions of the perirhinal and parahippocampal cortices, as well as the major cortical areas described in this study.

Perirhinal and parahippocampal cortices. The perirhinal cortex is composed of a smaller, medially situated area 35 and a larger, laterally situated area 36 (Fig. 1). For most of its rostrocaudal extent, area 35 is confined to the fundus and lateral bank of the rhinal sulcus. At the extreme rostral extent of the entorhinal cortex, area 35 extends slightly onto the medial bank of the rhinal sulcus. Area 36 is located just lateral to area 35 and has been parceled into five subdivisions. Area 36d (the dorsal subdivision of area 36) is located at the most rostral and dorsal extent of the perirhinal cortex and makes up approximately the dorsal one-third of what is typically referred to as the temporal pole (area 38 of Brodmann, 1909; area TG of Von Bonin and Bailey, 1947). Caudally, adjacent to area 36d, is area 36r (rostral subdivision of area 36). Area 36r is further subdivided into 36rm (rostrom...
Area 36rm is situated lateral to area 35, is relatively narrow in the mediolateral axis, and is bordered laterally along its full rostrocaudal extent by area 36rl. Area 36rl is the largest of the subdivisions of area 36. At its most rostral and dorsal extent, it makes up

approximately the ventral two thirds of the medial aspect of the temporal pole. Ventrally, area 36rl is situated at approximately the same level as the rostral one third of the entorhinal cortex. The caudal extreme of the perirhinal cortex is called area 36c (caudal subdivision of area 36) and is further subdivided into area 36cm (caudomedial subdivision of area 36) and area 36cl (caudolateral subdivision of area 36).

The parahippocampal cortex is caudally adjacent to both the entorhinal and the perirhinal cortices. It is made up of a smaller, medially situated area TH and a larger, laterally situated area TF. Area TF has been further sub-
divided into areas TFm (medial subdivision of area TF) and TFI (lateral subdivision of area TF). Area TFI is bounded laterally by areas TE and TEO and caudally by area OA (Von Bonin and Bailey, 1947), also referred to as area V4 (Zeki, 1971). For further cytoarchitectonic information on the perirhinal and parahippocampal cortices, see Suzuki and Amaral (2002).

**Areas TE and TEO.** Unimodal visual areas TE and caudally adjacent area TEO form a wide band of cortex bordered medially by area 36 and area TF, and bordered laterally by the fundus of the superior temporal sulcus. We adopted the terms TE and TEO for the larger subdivision spanning the ventromedial region bounded medially by the perirhinal and parahippocampal cortices and bounded laterally by the ventral lip of the superior temporal sulcus. This region previously has been subdivided into areas TE1, TE2, and TE3 (Seltzer and Pandya, 1978). It should be noted that the medial half of area TE1 of Seltzer and Pandya (1978) corresponds approximately to the lateral half of what we have labeled area 36 of the perirhinal cortex. We refer to the cortex lining the ventral bank of the superior temporal sulcus as the STSv, which includes areas TTea and TEM of Seltzer and Pandya (1978).

**Superior temporal sulcus.** The dorsal bank and fundus of the superior temporal sulcus (STS) are polymodal-associational areas (Seltzer and Pandya, 1978; Bruce et al., 1981; Baylis et al., 1987). This region, also referred to as the superior temporal polysensory area, or STP (Bruce et al., 1981), corresponds roughly to areas IPa, PGa, TPO, and TAA of Seltzer and Pandya (1978). We have labeled the dorsal bank and fundus of the superior temporal sulcus STSd and STSF, respectively.

**Superior temporal gyrus.** Much of the caudal portion of the superior temporal gyrus (STG) is auditory association cortex (Pandya et al., 1969; Merzenich and Brugge, 1973; Pandya and Sanides, 1973), whereas the rostral portion of STG also contains cells responsive to visual stimuli (Baylis et al., 1987). Furthermore, approximately the rostral half of the STG has direct connections with the entorhinal cortex, whereas more caudal regions do not (Insausti et al., 1987). Thus, although we recognize the differences between rostral and caudal STG, because of the difficulty in distinguishing these subdivisions on cytoarchitectonic grounds, we have labeled the entire region STG on the unfolded maps.

**Frontal lobe.** We have used the cytoarchitectonic description and nomenclature of Walker (1940) with slight modifications (Carmichael, 1993).

**Insular cortex.** We have used the cytoarchitectonic description and nomenclature of Jones and Burton (1976) for these areas.

**Cingulate and retrosplenial cortices.** The nomenclature for the rostral regions of the cingulate cortex (areas 24, 25, and 32) has been derived from the works of Pandya et al. (1981) and Vogt (1985) as adapted by Insausti et al. (1987). For the caudal portion of the cingulate cortex and the retrosplenial cortex, we have used the cytoarchitectonic description and nomenclature of Kobayashi and Amaral (2000). Briefly, the dorsal bank of the callosal sulcus and the anterior surface of the caudomedial lobule are covered by the retrosplenial cortical areas 29 and 30, whereas most of the medial surface of the posterior cingulate gyrus and the ventral bank of the posterior cingulate sulcus consist of area 23. On the ventral surface of the caudomedial lobule, we also defined a transitional zone, area 30v, located between the retrosplenial cortex and the prestripate visual cortex (Kobayashi and Amaral, 2000).

**Posterior parietal cortex.** The divisions of the posterior parietal lobe have been derived from Brodmann’s original description (Brodmann, 1909) as elaborated by Andersen et al. (1990).

**Description of the injection sites**

Figure 1 presents an unfolded map of the perirhinal and parahippocampal cortices to illustrate the size and location of the 15 anterograde and 4 retrograde tracer injections analyzed in this study. Figure 2 presents photomicrographs of the injection sites of the cases for which unfolded maps were constructed.

**3H-AA injections in area 36 are located at diverse mediolateral and rostrocaudal positions.** Starting rostrally, the injection in case DM-42 involves a large mediolateral extent of area 36d and the rostral portion of area 36r. The injection in M-15-98 is located in the medial part of the rostral portion of area 36r. The injection in M-7-92 involves the lateral aspect of area 35 and expands laterally into the medial portion of area 36r. The injection in M-6-92 occupies a mid- to lateral portion of rostral area 36r. The injection in M-7-92 is located at the lateral border of the caudal portion of area 36r. The injection in M-1-92 involves the lateral aspect of area 35 and expands laterally into the medial part of the caudal portion of area 36r. The injection in M-6-91 involves the lateral aspect of area 36rl, at the transition between area 36rl and 36cl. The injection in M-7-91 involves the mid- to mediolateral portion of area 36rl and extends into 36c. The injection in M-12-91 involves the mid- to mediolateral portion of area 36rl and extends into 36c. It partially overlaps with M-7-91 but extends further rostrally and medially than injection M-7-91. The injection in M-1-88 involves the medial and mid- to mediolateral portion of the rostral part of area 36c. It also partially overlaps with M-7-91 and extends further caudally. It also extends medially into the caudal portion of area 35. The injection in M-8-91 involves the mid- to mediolateral portion of caudal area 36c.

**3H-AA injections in area TF are located at different rostrocaudal positions.** The injection in M-13-91 is located in the rostral part of area TF in a mediolateral position. The injection in M-2-90 is located in a position very similar to M-13-91. The injection in M-14-91 is located at a mid-rostrocaudal and mid- to mediolateral portion of area TF. The injection in M-15-91 is also located at a mid- to mediolateral level but in the caudal portion of area TF.

**Retrograde tracer injections in the perirhinal and parahippocampal cortices.** The WGA-HRP injection in case M-15-98 was made through the same pipette as the 3H-AA so that the injection sites are superimposed. The injection is located in the medial portion of rostral area 36r. The FB injection in M-7-91 is located slightly more rostrally and medially than the 3H-AA injection in this case and involves the medial part of the most caudal portion of area 36r. The DY injection in case M-8-91 involves the lateral portion of area 36c and is located more rostrally and more laterally than the 3H-AA injection. The DY injection in M-2-90 is located slightly more laterally.
than the ³H-AA injection and involves the lateral part of the rostral portion of area TF.

Efferent and reciprocal projections of the perirhinal and parahippocampal cortices

We describe the organization and density of the efferent projections from the perirhinal and parahippocampal cortices to the neocortex in a manner similar to our description of the cortical afferents to these cortices (Suzuki and Amaral, 1994a). The data are typically presented on unfolded cortical maps (Fig. 3). The intensity of labeling was estimated visually and coded in four different levels: 0, no labeling; 1, low labeling; 2, moderate labeling; and 3, heavy labeling. This coding system provides a qualitative impression of the magnitude of the projections to each of the innervated areas. We also investigated the reciprocal...
ity of the connections between the perirhinal and parahippocampal cortices and the neocortex. This description derives from four cases with dual injections of anterograde and retrograde tracers placed at the same site or in close proximity in the same animal, as well as from the comparison between numerous independent anterograde and retrograde tracers cases from different animals. Finally, we describe the laminar organization of anterogradely labeled fibers and terminals in the neocortex.

**Temporal lobe**

**Efferent projections.** Anterograde tracer injections placed throughout the rostrocaudal and mediolateral extents of the perirhinal cortex (Figs. 4, 5, 6, 9, 11, 12) result in a similar pattern of efferent projections to the temporal lobe. Area 36 projects heavily to the unimodal visual area TE. The distribution of anterogradely labeled fibers and terminals in area TE, however, exhibits a subtle mediolateral topography. Heavy projections are observed medially in area TE, near the anterior medial temporal sulcus and moderate to light projections are observed in the more lateral portions of area TE. Similarly, rostral portions of the ventral bank of the STSv receive light to moderate projections from area 36. Area 36 also gives rise to more restricted albeit consistent, light to moderate projections to the rostral and medial portion of area STSd and to the most rostral aspect of the fundus of the superior temporal sulcus (STSf). There are few, if any, projections from the perirhinal cortex to the
cortex of the superior temporal gyrus (STG). In only two cases (M-6-92 and M-6-91), where the injections are located in the rostral and lateral part of area 36, do we observe labeled fibers in the superior temporal gyrus (Figs. 4, 6).

The pattern of projections from the parahippocampal cortex is very different from the perirhinal cortex pattern (Figs. 7, 8, 13). First, there are only very diffuse and light projections from area TF to area TE. Area TF does, however, give rise to light to moderate projections to the more medial aspect of area TEO near the occipital temporal sulcus. These light to moderate projections continue caudally into area V4. Area TF also projects lightly to the ventral bank of the superior temporal sulcus (STSv). One of the strongest temporal lobe projections of area TF is to the dorsal bank of the superior temporal sulcus (STSd) and to the cortex of the superior temporal gyrus (STG).

**Reciprocal projections.** There are systematic differences between the distributions of retrogradely labeled cells and anterogradely labeled fibers and terminals in the temporal lobe after tracer injections in area 36 (Fig. 9, 11, 12; Table 1). Although area 36 sends relatively meager projections to the rostral STSv and STSd, it receives projections from a substantially larger portion of these areas. As illustrated for case M-15-98 (Fig. 9), the projections from the superior temporal sulcus to area 36r originate from a more extensive region than that receiving input from area 36r. This finding is particularly obvious in the caudal portion of STSd. In contrast, area 36r sends heavier and more widespread projections to the unimodal areas TE and TEO than

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**Fig. 5.** M-12-91, ^3^H-AA injection in area 36r/c. Two-dimensional, unfolded maps of the frontal lobe (A), the insular cortex (B), the cingulate and retrosplenial cortices (C), and the temporal lobe (D), indicating the distribution and intensity of fiber and terminal labeling in the neocortex after anterograde tracer injection in the mid-mediolateral portion of area 36r and extending slightly into 36c. The different shades of gray represent the different intensities of anterograde labeling: light gray, low labeling; medium gray, moderate labeling; dark gray, heavy labeling; black, injection site. For abbreviations, see Fig. 3. Scale bar = 2 mm in D (applies to A–D).
it receives. These projections reach more lateral aspects of area TE as well as more caudal aspects of area TEO than those that project to area 36r (Fig. 9; Table 1). This pattern is even more striking for injections involving more caudal aspects of area 36 (Figs. 11, 12; Table 1). Note that there are large portions of areas TE, TEO, and V4 that receive inputs from, but do not generate projections to, area 36 (shown in green on the unfolded maps).

In contrast to the projections of the perirhinal cortex, the connections between area TF and the temporal lobe are generally more reciprocal (Fig. 13). Comparison of Figures 7, 8 and 13 of the present study and Figure 12 of Suzuki and Amaral (1994a), however, indicates that the projections between the temporal lobe and the parahippocampal cortex are not entirely reciprocal (see also Table 1). Area TF, for example, appears to receive more projections from the rostral parts of STSv and STSd than it sends to these areas. Conversely, area TF gives rise to heavier projections than it receives to caudal areas of the superior temporal sulcus. Area TF also projects to a wider portion of the unimodal visual cortex at the border between TE and STSv than that projecting to it.

**Frontal lobe**

**Efferent projections.** The efferent projections from the perirhinal cortex to the frontal lobe are generally light and limited to the lateral and medial orbitofrontal cortex, areas 12, 11, and 13 (Figs. 4, 5, 6, 9, 11, 12). Only in case M-8-91, which had an injection in area 36c, were there isolated projections more dorsally in area 45 (Fig. 12). The parahippocampal cortex projections to the frontal lobe are both more widespread and more substantial...
than the perirhinal cortex projections to these areas. Area TF sends at least light projections to practically all areas, including areas 9, 46, and 45 of the dorsolateral prefrontal cortex, areas 12, 11, and 13 of the orbital prefrontal cortex and areas 14 and 10 of the ventral prefrontal cortex. The most prominent of these projections are directed to areas 9 and 46 dorsolaterally and areas 11 and 13 of the orbitofrontal cortex.

**Reciprocal projections.** More of the cortical surface of the frontal lobe projects to area 36 than receives projections from it (Fig. 9, 11, 12; Table 1). The perirhinal cortex sends only light projections to a limited number of areas of the orbitofrontal cortex, mainly areas 12, 11, and 13. In experiment M-15-98, in which H-AA and WGA-HRP were injected through the same pipette into area 36r, only a very small portion of the frontal cortex contained both anterograde and retrograde labeling in the same or adjacent columns of cortex (Figs. 9, 10).

In contrast to the perirhinal-frontal interconnections, the distribution of afferent and efferent regions for the frontal lobe - area TF connections appears to be more overlapping (Figs. 13, 14; Table 1).

**Insular cortex**

**Efferent projections.** Injections in all portions of the perirhinal cortex lead to labeled fibers and terminals throughout areas Ig, Id, and Ia (Figs. 4, 5, 6, 9, 11, 12). Fewer fibers and terminals are observed in the parainsular cortex (Pi). In two cases (M-7-91 and M-15-98), isolated fibers were observed dorsal to the superior limiting sulcus in area SII. The distribution of the perirhinal projections to the insular cortex differs slightly depending on the
rostrocaudal level of the injection site. Injections located rostrally lead to moderately dense projections to Ig, Id, and Ia (Figs. 4, 5, 9). More caudal levels of the perirhinal cortex project primarily to areas Id and Ia and only lightly to area Pi (Figs. 6, 12). Area TF gives rise to moderately heavy projections to areas Ia, Id, and Pi, but none to area Ig (Figs. 7, 8, 13).

**Reciprocal projections.** As in the frontal cortex, more of the insular cortex projects to area 36r than receives a projection from it (Fig. 9, 11; Table 1). The parainsular cortex (area Pi), in particular, contributes more projections to the perirhinal cortex than it receives. Although the parahippocampal cortex receives robust projections from all areas of the insular cortex (Ia, Id, Ig, Pi), it does not project to the granular insular cortex (Ig; Fig. 13; Table 1).

**Cingulate and retrosplenial cortices**

**Efferent projections.** The perirhinal cortex sends light to moderate projections to the ventral portion of the caudal half of area 24 and very sparse projections to area 23 (Figs. 4, 5, 6, 9, 11, 12). There are no projections to areas 25 or 32 or any portion of the retrosplenial cortex (areas 23, 29, 30).

Area TF projects to areas 25 and 32 and more heavily to the ventral portion of area 24 (Figs. 7, 8, 13). Unlike the perirhinal projections, area TF projects preferentially to the rostral half of area 24. In addition, the parahippocampal cortex gives rise to light to moderate projections to area 29 and moderate to heavy projections to areas 30, 23, and 23v of the retrosplenial cortex.

Fig. 8. M-15-91, "H-AA injection in area TF. Two-dimensional, unfolded maps of the frontal lobe (A), the insular cortex (B), the cingulate and retrosplenial cortices (C), and the temporal lobe (D), indicating the distribution and intensity of fiber and terminal labeling in the neocortex after anterograde injection in the caudal mediolateral portion of area TF (transition of areas TFm and TFf). The different shades of gray represent the different intensities of anterograde labeling: light gray, low labeling; medium gray, moderate labeling; dark gray, heavy labeling; black, injection site. For abbreviations, see Fig. 3. Scale bar = 2 mm in D (applies to A–D).
Reciprocal projections. In contrast to the frontal and insular connections, the perirhinal cortex gives rise to heavier and more extensive projections to the cingulate cortex than it receives (Figs. 9, 11, 12; Table 1). In particular, area 36 projects more heavily and over a larger portion of area 24 than that projecting to area 36. Moreover, the distribution of anterogradely labeled fibers and terminals seems to reach preferentially the caudal part of area 24 (Figs. 9, 11, 12), whereas retrogradely labeled cells are also found in the more rostral aspect of area 24 (Fig. 9).

There appears to be more of a balance of the afferent and efferent connections between the parahippocampal cortex and the cingulate and retrosplenial cortices than between the perirhinal cortex and these cortices. By comparing maps of afferent and efferent projections, it is clear, however, that there are slightly more projections from the parahippocampal cortex to the cingulate and retrosplenial cortices than projections from these cortices to area TF (Fig. 13; see also Table 1).

Posterior parietal cortex

Efferent projections. There are no projections from the perirhinal cortex to the parietal cortex. All injections located in area TF, in contrast, result in light to moderate labeling in area 7a and LIP (Fig. 14).

Reciprocal projections. The distribution of terminal labeling in the parietal cortex mirrors the distribution of retrogradely labeled cells after injections in area TF (Fig. 14). A comparison of the distribution of anterogradely
The pattern of labeled terminals and fibers observed in this study with the distribution of retrogradely labeled cells of this study and the cases that we described previously (Suzuki and Amaral, 1994a) indicates that the connections between the parahippocampal cortex and the parietal cortex are highly reciprocal.

**Laminar organization of the efferent projections from the perirhinal and parahippocampal cortices to the neocortex**

The efferent projections from the perirhinal and parahippocampal cortices are primarily directed to the superficial layers of the neocortex and largely avoid layer IV. In all areas of the cortex receiving heavy projections, fibers and terminals are distributed throughout all layers except for layer IV. This pattern of termination is characteristic of projections of the feedback type (Felleman and Van Essen, 1991; Rockland, 1994, 1997; Rockland and Knutson, 2000). However, there are differences between the laminar organization of the fibers and terminals in the different recipient cortical areas.

**Temporal lobe.** Projections directed to visual processing areas TE, TEO, STSv, and V4, terminate predominantly in layer I. Moreover, in most of these areas, the labeling is distributed continuously over large portions of the recipient cortex, i.e., there is no patchy or columnar organization of the terminals. In areas such as the STS, lateral and caudal area TE, and area TEO (areas that receive light to moderate density projections), terminal labeling is mainly in layer I and can extend continuously from the anterior medial temporal sulcus to the superior temporal sulcus (Fig. 15B,F). In addition to the continuous labeling observed in layer I, terminal labeling tends to show a patchy organization throughout the other cortical layers (except for IV) in the heavily labeled medial aspect of area TE (Fig. 15D,E).

In multimodal areas such as the superior temporal gyrus, labeled fibers and terminals are distributed throughout all superficial layers, in particular layers II and III, with relatively fewer fibers and terminals in layer I (Fig. 16A). However, the labeling is uniformly patchy or columnar. Figure 16B,C shows a similar pattern of laminar organization in STSd. In areas receiving heavy projections, the laminar distribution of the projections extends throughout all layers, except for layer IV.

**Frontal lobe.** The projections from the perirhinal and parahippocampal cortices to the prefrontal cortex terminate predominantly in layers I, II, and III (Fig. 17A–D).

**Insular cortex.** In the granular insular cortex (Ig), projections from the perirhinal cortex are directed more strongly towards layer I (Fig. 17E). In the parainsular cortex, in contrast, projections from the perirhinal and parahippocampal cortices terminate predominantly in the superficial layers II and III, with fewer fibers and terminals in layer I (Fig. 17F).

**Cingulate and retrosplenial cortices.** Like other nonvisual association cortices, the efferent projections of the perirhinal and parahippocampal cortices terminate predominantly in patches in the superficial layers of the cingulate and retrosplenial cortices (Fig. 16D,E). There is heavy labeling in the supragranular layers I, II, and III, but very light labeling in the infragranular layers V and VI.

**Parietal cortex.** The laminar organization of the projections from the parahippocampal cortex to the parietal cortex is similar to that observed in other nonvisual association cortices. Anterograde tracer injections in area TF lead to moderate labeling in the superficial layers (II and III) of area 7, with lighter labeling in layer I (Fig. 16F). The pattern of labeled terminals and fibers in the infragranular layers is typical of cortical areas receiving relatively strong projections.

**DISCUSSION**

We have attempted to present a comprehensive analysis of the cortical efferents of the perirhinal and parahippocampal cortices of the macaque monkey. These studies have provided three types of new information.

First, we have confirmed and extended early work (Van Hoesen, 1982) indicating that the perirhinal and parahippocampal cortices project to widespread areas of the cortex, including both unimodal and polymodal association areas. These efferent projections reciprocate, in part, the afferent projections from the neocortex (Suzuki and Amaral, 1994a). However, there are noticeable differences in the degree of reciprocity of the connections between the perirhinal and parahippocampal cortices and certain areas of the neocortex, particularly the frontal and temporal lobes.

Second, based on their pattern of termination, it appears that all the efferent cortical projections of the
perirhinal and parahippocampal cortices are projections of the feedback-type. Indeed, these projections are primarily directed to the superficial layers of the neocortex and largely avoid layer IV. We found, however, that unimodal visual cortex receives a different pattern of innervation than polymodal association areas.

Third, we have found that the perirhinal and parahippocampal cortices differ in their pattern of reciprocal connections with the neocortex. The perirhinal cortex has asymmetric projections with several cortical areas, whereas the projections between the parahippocampal cortex and the neocortex are more reciprocal. It is important to note that the differences between the patterns of cortical afferents and efferents that we describe in this study cannot be explained simply by differences in sensitivity of the anterograde and retrograde tracer methods or

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**Fig. 10.** M-15-98, 3H-AA/WGA-HRP injection in area 36r. Line drawings of representative coronal sections arranged from rostral (A) to caudal (F) from case M-15-98 (see also Fig. 9), which contained a combined anterograde and retrograde tracer injection in the medial part of the rostral portion of area 36r (area 36rm). Anterogradely labeled fibers and terminals are represented in green, retrogradely labeled cells in red. For abbreviations, see Fig. 3. Scale bar = 2 mm in F (applies to A–F).
by differences in the size of the injections. Indeed, even for the cases with both anterograde and retrograde tracers placed at the same site or in close proximity, we observe some striking differences in the distribution of anterograde and retrograde labeling. Some cortical areas receive projections from area 36 for instance, but do not project to it, whereas other areas (in the same case) show the reverse pattern. In none of the cases did we observe the distribution of one tracer overlapping completely with the distribution of the other tracer. Nor was it typical that one tracer demonstrated a large afferent or efferent field and the other tracer demonstrated a smaller area contained within the larger area of labeling. Such a pattern of labeling between the two tracers would have suggested a characteristic difference in sensitivity or regular variations in the size of the two injections. This was clearly not the case in our experiments.

In the remainder of the discussion, we first compare our findings with previous reports. We then discuss the possible functional significance of the various degrees of reciprocity and implications for current theories of memory consolidation.

Projections to the temporal lobe
Visual areas TE, TEO, STSv, V4. Our results extend previous findings showing strong projections from the perirhinal and parahippocampal cortices to the unimodal visual areas TE, TEO, STSv, and V4. Distler et al. (1993) found labeled neurons in the perirhinal and parahippocampal cortices after injections of retrograde tracer in

Fig. 11. M-7-91, $^{3}$H-AA/FB injections in area 36r/c. Two-dimensional, unfolded maps of the frontal lobe (A), the insular cortex (B), the cingulate and retrosplenial cortices (C), and the temporal lobe (D), indicating the distribution of anterogradely labeled fibers and terminals and retrogradely labeled cells in the neocortex after anterograde and retrograde tracer injections in area 36r/c. The $^{3}$H-AA injection involved the caudal part of mid-medial lateral portion of area 36r and the rostral aspect of the mid-medial lateral portion of area 36c (transition between 36rl and 36cl). The FB injection was located slightly more rostrally and medially than the $^{3}$H-AA injection and involved the medial part of the most caudal portion of area 36r (area 36rm). Anterogradely labeled fibers and terminals are represented in green, retrogradely labeled cells in red; columns of cortex that contained both anterograde and retrograde labeling are indicated in black. For abbreviations, see Fig. 3. Scale bar = 2 mm in D (applies to A–D).
most areas of TEO. Our results indicate that area 36 projects to a more widespread portion of area TEO than area TF does. Consistent labeling was observed in all areas of TEO after injections in area 36, whereas only the most medial aspect of TEO contained labeled fibers after injections in area TF. The projections from the parahippocampal cortex to area TEO, thus, appear to be more limited than previously thought (Van Hoesen, 1982; Shiwa, 1987; Webster et al., 1991). Our results also confirm and extend previous findings showing projections from the parahippocampal gyrus to area V4 (Tanaka et al., 1990; Steele et al., 1991). These projections arise predominantly from area TF. In contrast to a previous report by Rockland and Van Hoesen (1994), we do not observe any projections to area V1 from area 36 or TF.

One of the most striking findings of this study is that the connections between the perirhinal and parahippocampal cortices and the unimodal visual areas TE, TEO, and V4 are not entirely reciprocal. By using both anterograde and retrograde tracer injections in areas TE and TEO, Webster et al. (1991) reported reciprocal connections between area TE and area 36. They noted, however, that area TEO does not project to areas 36 and TF in adult animals. Our findings reveal that both the perirhinal and parahippocampal cortices receive projections from areas TE and TEO and send feedback projections to both of these areas.
Area TF exhibits relatively symmetrical reciprocal projections with the medial portion of areas TE and TEO, whereas area 36 projects to more widespread portions of areas TE (more laterally) and TEO (more caudally) than it receives projections from. The patterns of terminations observed in this study, and the laminar organization of the cells of origin described in Webster et al. (1991), indicate that the efferent projections from the perirhinal and parahippocampal cortices to unimodal areas are projections of the feedback type (Felleman and Van Essen, 1991; Rockland, 1994).

Superior temporal polymodal areas STSf and STSd.

The projections from the perirhinal cortex to areas STSf and STSd show a clear rostrocaudal organization. Area 36 is interconnected with only the most rostral aspect of STSd, corresponding largely to area TPO1 of Seltzer and Pandya (1989). Interestingly, amongst the different subdivisions of area TPO, only TPO1 projects to, and receives fibers from, area IPa, which in turn has reciprocal connections with area TEa (a unimodal visual area corresponding largely to our area STSv). More caudally, area TPO (TPO2-4) has reciprocal connections laterally with area TAA and medially with
area PGa which, in contrast to area IPa, does not have any reciprocal connections with area TEa (Seltzer and Pandya, 1989). Our results suggest that the perirhinal cortex is interconnected with only the rostral aspect of STSd, a polysensory area that has reciprocal connections with cortical areas involved in visual information processing (Seltzer and Pandya, 1989). Unlike the perirhinal to TE/TEO connections, the perirhinal cortex appears to project to a much more restricted area of the anterior superior temporal sulcus than it receives inputs from. However, these projections are also characteristic of projections of the feedback type, terminating primarily in the superficial layers. Our observations are consistent with the results of Seltzer and Pandya (1994) who observed labeled cells in layer V of the parahippocampal cortex after injection of retrograde tracer in area TPO1.

Superior temporal gyrus. Tranel et al. (1988) previously showed that area TH of the parahippocampal cortex projects to the superficial layers I–III of the posterior portion of the STG (area Tpt). In our studies, we found that injections in area TF produced significant labeling along the entire rostrocaudal extent of STG. The projections between STG and area TF are highly reciprocal. Our results together with those of Tranel et al. (1988) indicate that the efferent projections from the parahippocampal cortex to the STG are characteristic of projections of the feedback type.
Projections to the frontal lobe

Consistent with previous findings (Goldman-Rakic et al., 1984; Morecraft et al. 1992; Carmichael and Price, 1995; Barbas et al., 1999), we found that the projections from the perirhinal cortex to the frontal cortex are generally light and restricted to the lateral and orbital prefron-
tal cortex, areas 12, 11, and 13. In contrast, the projections from the parahippocampal cortex to the frontal lobe are more widespread and reach the dorsolateral prefrontal cortex, the orbital prefrontal cortex, and the ventral prefrontal cortex. Using retrograde tracer injections in the frontal cortex, Carmichael and Price (1995) showed that areas TF and TH send projections to area 11m, 13a, 14r, and 14c. Similarly, Morecraft et al. (1992) found that...

Fig. 16. Darkfield photomicrographs illustrating different patterns of fiber and terminal labeling in the cortex of the superior temporal gyrus, the cortex surrounding the superior temporal sulcus, the cingulate cortex, and the parietal cortex after injections of 3H-AA anterograde tracer in the perirhinal and parahippocampal cortices. A: Heavy labeling in area STG after an injection in caudal area TF (case M-15-91). B: Moderate labeling in area STSd after an injection in area TF1 (case M-14-91). C: Heavy labeling in area STSd after an injection in area 36cl (case M-7-91). D: Heavy labeling in area 24 of the anterior cingulate cortex after an injection in rostral area TF (case M-2-90). E: Moderate labeling in areas 23/30 of the retrosplenial cortex after an injection in area TF1 (case M-14-91). F: Heavy labeling in area 7 after an injection in rostral area TF (case M-2-90). Scale bar = 0.5 mm in A (applies to A–F).
several areas of the orbitofrontal cortex, including areas POdg and OFg, receive significant projections from areas TF and TH and the cortex of the temporal pole (which we include as perirhinal areas 36d and 36r). The location of the retrograde tracer injection site in cases 2 (POdg) and 3 (OFg) of Morecraft et al. (1992) seem to include mainly portions of areas 11 and 13 and, thus, are consistent with our results and those of Carmichael and Price (1995). Our findings also confirm the data of Goldman-Rakic et al. (1984) who showed that area 46 receives projections from

Fig. 17. Darkfield photomicrographs illustrating different patterns of fiber and terminal labeling in the frontal cortex and the insular cortex after injections of $^{3}$H-AA anterograde tracer in the perirhinal and parahippocampal cortices. A: Moderate labeling in area 11 of the orbital prefrontal cortex after an injection in area TF1 (case M-14-91). B: Heavy labeling in area 13 of the orbital prefrontal cortex after an injection in area TF1 (case M-14-91). C: Moderate labeling in area 13 of the orbital prefrontal cortex after an injection in area TF1 (case M-14-91); image rotated 45° counterclockwise. D: Moderate labeling in area 46 of the dorsal prefrontal cortex after an injection in area TF1 (case M-14-91). E: Moderate labeling in area Ig of the insular cortex after an injection in area 36cl (case M-7-91). F: Heavy labeling in area Pi of the insular cortex after an injection in area 36cl (case M-7-91). Scale bar = 0.5 mm in A (applies to A–F).
the parahippocampal cortex, mainly area TF. The projections between area TF and the frontal lobe are highly reciprocal. Indeed, all areas of the frontal lobe projecting to area TF receive feedback projections from this area. The laminar organization of the efferent connections of areas 36 and TF described in this study is consistent with a previous study indicating that efferent fibers from area 36 terminate preferentially in the upper layers of area 13 (Rempel-Clower and Barbas, 2000). Our results with anterograde tracers are also consistent with the results of Carmichael and Price (1995), who found retrogradely labeled neurons concentrated in layer V and VI of the parahippocampal cortex after injections of retrograde tracers in the frontal lobe. Similarly, Goldman-Rakic et al. (1984) found that after retrograde tracer injection in area 46, labeled neurons in area TF and TH are predominantly observed in layers V and VI. In both studies, fewer retrogradely labeled neurons were observed in layer III. These patterns of terminations and the laminar organization of the cells of origin are consistent with projections of the feedback type (Felleman and Van Essen, 1991; Rockland, 1994).

**Projections to the insular cortex**

Our findings extend the results of previous reports indicating projections from the medial temporal lobe to the insula (Mufson and Mesulam, 1982; Carmichael and Price, 1995). The projections from the perirhinal and parahippocampal cortices to the insular cortex are characteristic of projections of the feedback type. However, these projections are not totally reciprocal, and not all areas projecting to areas 36 and TF receive feedback projections. Carmichael and Price (1995) observed retrogradely labeled cells in layers V and VI of the perirhinal cortex after retrograde tracer injection in all areas of the anterior agranular insular cortex (areas Iapm, Iam, Iai, and Ial). Similarly, Mufson and Mesulam (1982) observed numerous retrogradely labeled cells in the perirhinal cortex after tracer injection in areas Ia, Id, and relatively fewer labeled cells in the perirhinal cortex after injections in area Ig. However, in our study, we observed limited projections from area TF to the agranular insular cortex (area Ia), which were not revealed previously (Mufson and Mesulam, 1982; Carmichael and Price, 1995). Our analysis also indicates that area 36 projects equally to areas Ia, Id, and Ig, whereas the projections to the parainsular cortex are extremely meager. In contrast, area TF projects to areas, Ia, Id, and Pi, and does not seem to project to area Ig. To our knowledge, there were no previous observations concerning the projections from the perirhinal and parahippocampal cortices to the parainsular cortex.

**Projections to the cingulate and retrosplenial cortices**

Our results extend previously reported findings regarding the cortical afferents to the cingulate cortex (Vogt and Pandya, 1987). We find that the perirhinal projections terminate preferentially in the more caudal part of area 24, supporting further the idea of rostrocaudal differences in area 24. Parahippocampal projections, in contrast, terminate predominantly in the rostral part of area 24, areas 25 and 32, and in the posterior cingulate and retrosplenial cortices. All of the projections from the perirhinal and parahippocampal cortices terminate preferentially in the ventral aspect of the cingulate cortex. The projections from the perirhinal and parahippocampal cortices to the cingulate and retrosplenial cortices are characteristic of projections of the feedback type. In contrast to what was reported by Vogt and Pandya (1987), we do not find that labeling was preferentially directed to layer I after injection in area TF. In area 24, labeling seems to be equally distributed throughout all superficial layers (Fig. 17). In area 23, labeling is concentrated in layers II and III, with fewer terminals in layer I. As previously reported by Vogt and Pandya (1987), we also commonly observe labeling in layers V and VI that can be associated with axons en passage. The retrograde cases presented by Vogt and Pandya (1987) further confirm that the projections from area TH and TF to the cingulate cortex originate mainly in layer V and are, thus, characteristic of projections of the feedback type.

**Projections to the parietal cortex**

Our results confirm previous findings regarding the cortical afferents to the posterior parietal cortex (Cavada and Goldman-Rakic, 1989; Blatt et al., 1990). Blatt et al. (1990) showed that area LIP receives projections from area TF. Similarly, Cavada and Goldman-Rakic (1989) demonstrated that area 7a receives strong projections from the parahippocampal cortex, in particular from area TF. Our results indicate that area TF sends significant projections to both areas 7a and LIP, whereas there are essentially no projections from area 36 to the parietal cortex. The projections between area TF and the parietal cortex are highly reciprocal. Both areas of the parietal cortex that project to the parahippocampal cortex receive feedback projections. After a retrograde tracer injection in area 7a (see Figs. 7 and 9D of Cavada and Goldman-Rakic, 1989), the cells of origin of the projections from area TF and TH seem to be located in the deep layers, probably in layer V.

**Estimates of reciprocity**

To get a more quantitative appreciation of the extent of reciprocity of the interconnections between perirhinal and parahippocampal cortices and neocortex, we computed an "index of reciprocity" for cases with both anterograde and retrograde tracer injections. As discussed earlier, the present experiments examined the reciprocity of the connections at the area-to-area level and do not provide any information about whether one particular neuron, in one area, is reciprocally connected with another neuron, in a different area. The reciprocity index provides a quantitative evaluation of the relative strength of the afferent versus efferent projections between the perirhinal and parahippocampal cortices and various neocortical areas. The value of this index can be influenced by the absolute number of columns that contain either anterograde or retrograde labeling. Thus, variations in the sizes of the injections or differences in the sensitivity of the tracers could lead to differences between cases in the absolute value of the index for certain brain areas. However, the variations in the value of the index between different cortical areas within the same case are not influenced by the sizes of the tracer injections since they generate all afferent and efferent connections. In case M-7-91 for instance, an index value of ~1.00 for the STG provides a quantitative estimate showing that the STG sends projections to area 36r/c but does not receive any projections in return. In contrast, an index value of 0.91 for the lateral
part of TEO indicates that area 36r/c sends many more projections to area TEOI than it receives from it. In case M-15-98, an index value of 0.45 for area TEl indicates that area 36r sends more projections to the lateral half of area TE than it receives from this area. In comparison, an index value of 0.15 for area TEM indicates that area 36r receives almost as many projections from the medial half of TE as it sends to this area. Thus, the index provides quantitative estimates showing that area 36r is more reciprocally interconnected with the medial part of area TE than with the lateral part of TE. These examples illustrate how this index can be interpreted to evaluate the relative strength of the afferent versus efferent projections between the perirhinal and parahippocampal cortices and various neocortical areas.

Functional implications

The organization of the cortical efferent projections of the perirhinal and parahippocampal cortices has important implications for current theories of memory consolidation. These theories are based on the observation that long-term declarative memories are only initially dependent on the integrity of the medial temporal lobe (Teyler and DiScenna, 1986; Damasio, 1989; Alvarez and Squire, 1994; McClelland et al., 1995). Engrams or memory traces gradually become established, or “consolidated,” presumably in the neocortex and are eventually no longer dependent on the medial temporal lobe. This consolidation process is thought to depend on the feedback projections from the medial temporal lobe to the neocortex. Consistent with the idea that these projections are critical to the establishment of long-term memories, Higuchi and Miyashita (1996) have shown that lesions of the entorhinal and perirhinal cortices prevent the formation of mnemonic signals associated with learned visual paired associates in visual area TE.

Although the specific mechanisms by which these feedback projections act to consolidate neocortical memory traces remain unknown, an inherent assumption is that these projections are highly reciprocal. Proponents argue that neurons initially activated when information is first perceived, would then be stabilized as part of the network involved in storing the information. This general assumption is consistent with a large body of neuroanatomic data emphasizing the reciprocal nature of cortico-cortical projections (Van Hoesen, 1982; Felleman and Van Essen, 1991; Higuchi and Miyashita, 1996). Our anatomic findings, however, suggest a more complex pattern of cortico-cortical connectivity (see also Rockland et al., 1994; Salin and Bullier, 1995).

One particularly interesting observation is the contrast between the more highly reciprocal connections of the parahippocampal cortex compared with the more asymmetric connections of the perirhinal cortex. The perirhinal and parahippocampal cortices are considered to be at the same hierarchical level, i.e., the first stage, in the neocortical-hippocampal loop subserving memory consolidation (Lavenex and Amaral, 2000). However, the present findings suggest that, although the perirhinal and parahippocampal cortices are anatomically located at the same hierarchical level, they might play different roles in memory consolidation processes. An important characteristic that differentiates the perirhinal and parahippocampal cortices is their patterns of neocortical inputs and, thus, the kind of information reaching these two cortices. The parahippocampal cortex has a more point-to-point relationship with the cortical regions with which it interacts, whereas the perirhinal cortex has more asymmetrical cortical interconnections. The reason for this finding is not clear. Yet, it is possible that the different types of information processed by these two cortical areas necessitate different types of feedback projections to enable memory consolidation. Spatial information, reaching preferentially the parahippocampal cortex, might require more tightly reciprocal connections for consolidation, whereas visual object information reaching preferentially the perirhinal cortex might require more divergent feedback projections. It may also be that the perirhinal and parahippocampal cortices participate in perceptual processes that may be independent of their mnemonic functions (Murray and Richmond, 2001). If this is the case, then perhaps the different cortical relationships are essential for these functions and do not have strong implications for the consolidation process. Functional studies will be necessary, therefore, to further characterize and distinguish between the different kinds of information processing that takes place in the perirhinal and parahippocampal cortices.

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