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LIMBIC AND SENSORY CONNECTIONS OF THE INFERIOR PARIETAL LOBULE (AREA PG) IN THE RHESUS MONKEY: A STUDY WITH A NEW METHOD FOR HORSERADISH PEROXIDASE HISTOCHEMISTRY

MAREK-MARSEL MESULAM, GARY W. VAN HOESEN, DEEPAK N. PANDYA and NORMAN GESCHWIND

The Bullard and Denny-Brown Laboratories, Harvard Neurological Unit, Beth Israel Hospital, Boston, Mass. 02215 and Aphasia Research Center, Department of Neurology, Boston University Medical School, Boston, Mass. (U.S.A.)

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SUMMARY

The caudal part of the inferior parietal lobule (area PG) was injected with horseradish peroxidase (HRP) in 6 hemispheres of 5 rhesus monkeys. The retrograde transport of HRP resulted in the labeling of neurons in diverse cortical and subcortical areas. In cortex, labeled neurons were noted in prefrontal cortex (areas 8, 45, 46), in the banks of the intraparietal and superior temporal sulci, in medial parietal cortex, in cingulate cortex, in the retrosplenial area, in area TF and the caudal portions of the parahippocampal region. Subcortical sites with labeled neurons included the nucleus basalis of the substantia innominata, the claustrum, the pulvinar and intralaminar thalamic nuclei, the pretectal area, the nucleus locus coeruleus and the raphe nuclei. Although many of the labeled neurons were seen in layers IIIc and V, each cortical area had an individual laminar pattern of labeled neurons.

In these experiments, a benzidine dihydrochloride (BDHC) method was used which yields a blue reaction-product at sites containing HRP. BDHC affords superior visibility of labeled neurons, and a significant improvement in sensitivity when compared to a diaminobenzidine procedure in matching series of sections. Additional sections were also stained with a method which allows the simultaneous demonstration of HRP (blue) and acetylcholinesterase (reddish-brown). These revealed that virtually all substantia innominata (nucleus basalis) neurons which project to area PG are also rich in the enzyme acetylcholinesterase.

These afferents of PG may be classified into 'sensory association', 'limbic' and 'reticular' categories. It is argued that this arrangement of afferent imput may afford a convergence of limbic and sensory information in area PG and that this may subserve a significant function in the process of sensory attention.

INTRODUCTION

The anatomical and functional relationships of the inferior parietal lobule (IPL) are poorly understood. However, several lines of experimental and clinical evidence suggest that the IPL has a pivotal function in the complex sensory motor processes which underly 'attention'. For instance, unilateral ablations which involve the IPL of the monkey result in neglect of contralateral sensory stimuli[15,17,22]. Similarly, posterior parietal lesions in the right hemisphere of man often result in a state of contralateral inattentiveness which resembles the unilateral sensory neglect in the monkey[10,15,21,23,43]. Since it does not seem possible to explain such attentional deficits on the basis of elementary motor or sensory impairments alone, it is generally assumed that the posterior parietal cortex of both man and monkey coordinates the integration of complex sensory processes which are crucial for intact attention.

This assumption has gained support from experiments in which the activity of units in the IPL have been monitored in awake and behaving monkeys[25,45]. For instance, only few units in the IPL have been found to respond to elementary sensory stimulation in only one modality. On the other hand, many units were strongly activated when a desirable stimulus (food when hungry or liquid when thirsty) became the target of visual tracking, visual fixation, manual reaching or manipulation[25,45]. In some of the units which were related to manual reaching, the activity of the cell was found to be independent of the modality in which the cuing signal was presented to the animal[45]. Since these neurons may be related to the process of attention, these observations are consistent with the fact that IPL ablations cause deficits which are primarily attentional in nature.

The complex properties of IPL units are likely to depend on their anatomical connections. Furthermore, the set of contingencies which characterizes their response characteristics would suggest the presence of several categories of neural connections. First, it might be predicted that there would be an efferent outflow directed towards motor centers in order to initiate or inhibit the motor sequences which are necessary for attentive behavior. Secondly, afferents which convey extensively processed sensory information are essential in order to provide a comprehensive representation of the sensory space. Thirdly, it is reasonable to expect input from 'limbic' regions so that the motivational value of external events may be assessed. Information in sufficient detail to evaluate these anatomical postulates is presently not available.

The efferent projections from the IPL of the monkey have been described previously[9,29,53,61]. Although several sources have been noted[29,50,51,53,54,57], the afferent connections of the IPL have not been studied systematically. Such systematic studies of afferent connections within the central nervous system have become possible with the introduction of horseradish peroxidase (HRP) neurohistochemistry[36]. In this article, we would like to report experiments with HRP concerning the afferent connections of the IPL in the rhesus monkey. These results are based on a benzidine dihydrochloride (BDHC) method for HRP[41] which provides excellent visibility of labeled neurons and which also offers the distinct advantages of greater sensitivity and reliability when compared to a commonly used diaminobenzidine procedure.

METHODS

Six rhesus monkeys weighing 3–4 kg were used in these experiments. In 6 hemispheres of 5 monkeys, the caudal part of the IPL (area PG) was injected with HRP. The corpus callosum had previously been transected in one animal which received bilateral injections. One other animal with no HRP injection served as a histochemical control case and its brain was processed as in the other cases.

With the monkey under pentobarbital narcosis, the parieto-occipital region was exposed and the IPL was identified with reference to sulcal landmarks. A 10–20% aqueous solution of HRP (Sigma VI) (0.2–0.5 μl) was injected at an approximate rate of 0.04 μl/min through a 26-gauge Hamilton microsyringe mounted on a stereotaxic instrument. Three to four injections, each separated by 3–4 mm, were made under microscopic guidance within the target area at a depth of 1.5–2.5 mm below the pia mater. The total volume injected in any one case varied from 1.2 to 2.0 μl and the total weight of HRP injected in a single case varied from 0.4 mg to 0.12 mg. Following a 42–48 h survival, the monkey was anesthetized and perfused transcardially. The specific pattern of perfusion and fixation varied from experiment to experiment. Best results were obtained by starting the perfusion with 200–500 ml of slaine (21 °C) followed by 2 liters of fixative at 21 °C which contained 1.25% glutaraldehyde and 1% paraformaldehyde in an 0.1 *M* phosphate buffer at a pH of 7.4[20]. This was followed by further perfusion with 2 liters of the same buffer at 4 °C to which 10% sucrose had been added[58]. The brain was then removed and placed in the same buffer–sucrose solution for 24 h at 4 °C. At the end of this period, the brain was photographed and cut by a freezing microtome into 40 μm thick sections which were collected in the phosphate buffer.

In order to trace the retrograde transport of HRP, a benzidine dihydrochloride (BDHC) procedure was used which yields a clearly visible blue reaction-product at sites of HRP activity. This protocol was identical to procedure 8 described previously[41]. In this procedure, free-floating sections are presoaked for 20 min at 21 °C in a medium which contains 0.05% BDHC (practical grade, Sigma), 0.1% sodium nitroferricyanide and 30% ethanol. Each 100 ml of this medium contains 5 ml of 0.2 *M* acetate buffer at pH 5. After 20 min, H_2O_2 is added to the medium to reach a final concentration of 0.012% and the incubation is allowed to proceed for 25 min. The tissue is then transferred, without washing, to a stabilization bath at 0–4 °C. This bath contains 9% sodium nitroferricyanide, 50% ethanol and is buffered with acetate as above. At the end of the stabilization which proceeds for 20 min at 0 °C, the sections are washed in water, mounted onto glass slides subbed with chrome-alum, allowed to air-dry and counterstained with a 1% solution of neutral red. In some cases, matching sections were stained with thionin in order to facilitate the cytoarchitectonic identification of areas which contained cells labeled with HRP.

In order to study the acetylcholinesterase (AChE) content of the neurons which project to the IPL, matching sections were also processed so that HRP (blue) and AChE (reddish-brown) could be demonstrated simultaneously in the same tissue section[42]. Finally, in two of the experimental animals, matching sections were proces-

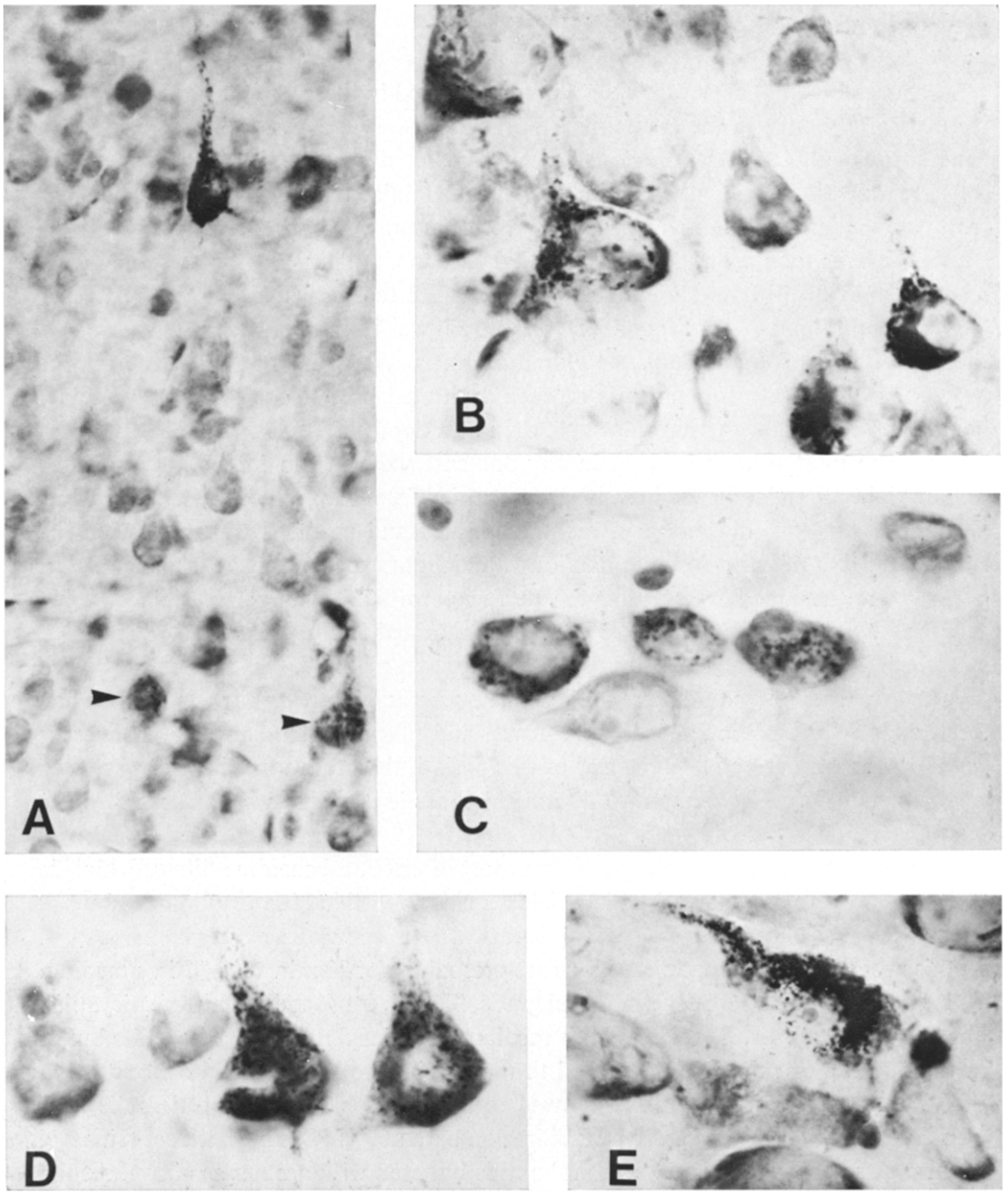

Fig. 1. Photomicrographs of labeled neurons in tissue processed with the BDHC method. A: three labeled neurons in the retrosplenial area of case 2. One heavily labeled neuron is seen just under the granular layer while two other lightly labeled neurons (arrows) are situated in the infragranular layers (× 587). B: four labeled neurons in the cingulate cortex of case 3 (× 898). C: three labeled neurons in layer V of area TF in case 5 (× 1053). D: two labeled neurons in layer III of area 46 in case 2 (× 982). E: a labeled neuron in the nucleus basalis of case 3 (× 702). All magnifications are given in reference to the final illustration size.

sed according to a commonly used diaminobenzidine (DAB) procedure which yields a brown reaction-product at sites of HRP activity[41]. These sections were used to compare the relative effectiveness of the two procedures in the visualization of the retrograde transport of HRP.

The distribution of neurons which contained HRP was charted with the aid of an X–Y plotter which was electronically coupled to the mechanical stage of a microscope.

RESULTS

The benzidine dihydrochloride procedure

In the procedure with benzidine dihydrochloride (BDHC) as the chromogen, a dark-blue reaction-product was formed at sites containing HRP activity. The tinctorial contrast among the white background, red perikarya and blue HRP reaction-product enabled the easy identification of even lightly labeled neurons under bright-field illumination (Figs. 1, 2). In addition to this improvement in visibility, the BDHC method also afforded increased sensitivity and reliability when compared to a diaminobenzidine (DAB) procedure. At virtually every site, sections processed with BDHC contained many more labeled cells than matching sections processed with DAB, even when the latter were examined under dark-field illumination. In some cortical areas such as the contralateral IPL in one case, this difference became very critical since the DAB procedure failed to visualize virtually any labeled cells whereas the BDHC method revealed 3–40 labeled neurons in matching sections. The difference at thalamic sites, although still significant, became less critical since a large population of labeled neurons could be discerned with either method. Moreover, areas such as the globus pallidus and substantia nigra, which are prone to artifactual labeling in the DAB method[71], were free of reaction-product following the BDHC method.

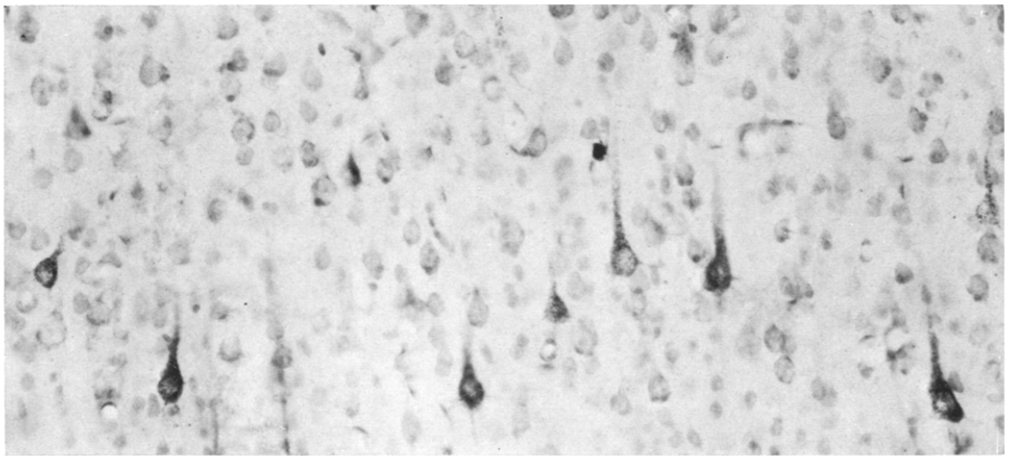

Fig. 2. This photomicrograph shows many labeled neurons in layer III of medial parietal cortex in case 1. The BDHC method makes these cortical neurons easily visible at this moderate magnification (× 350).

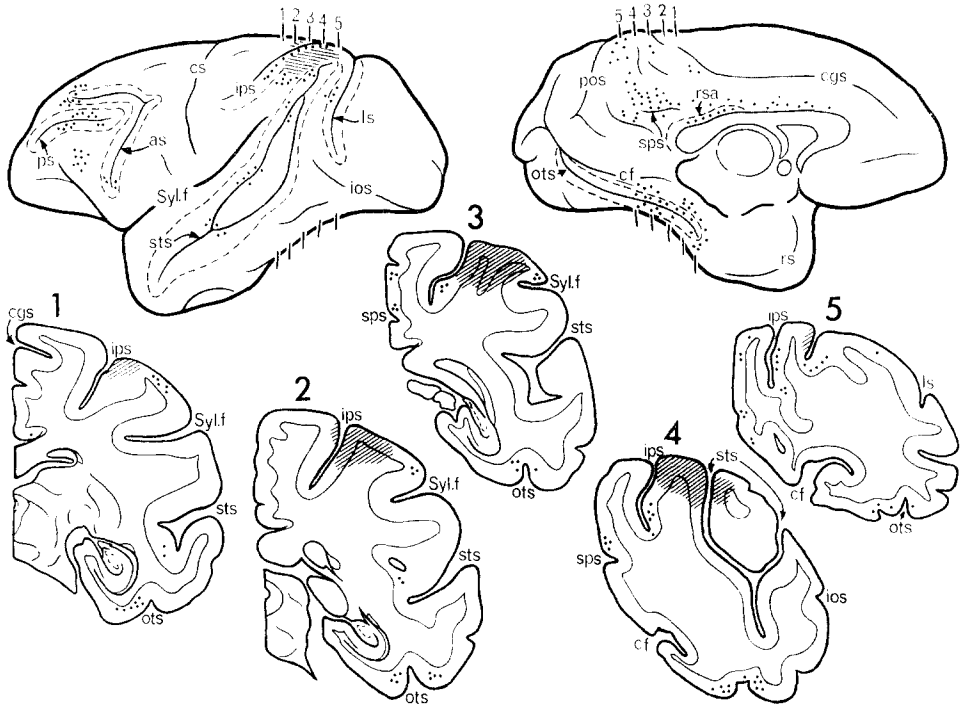

Fig. 3. Case 1. This figure depicts the topographical localization of the HRP injection (hatching) and the distribution of cortical neurons labeled with HRP (squares). The relative density of squares reflects the relative number of labeled neurons at each site. Each square represents many labeled neurons. The area between the dashed lines and the solid lines represent the cortex along the banks of the sulci.

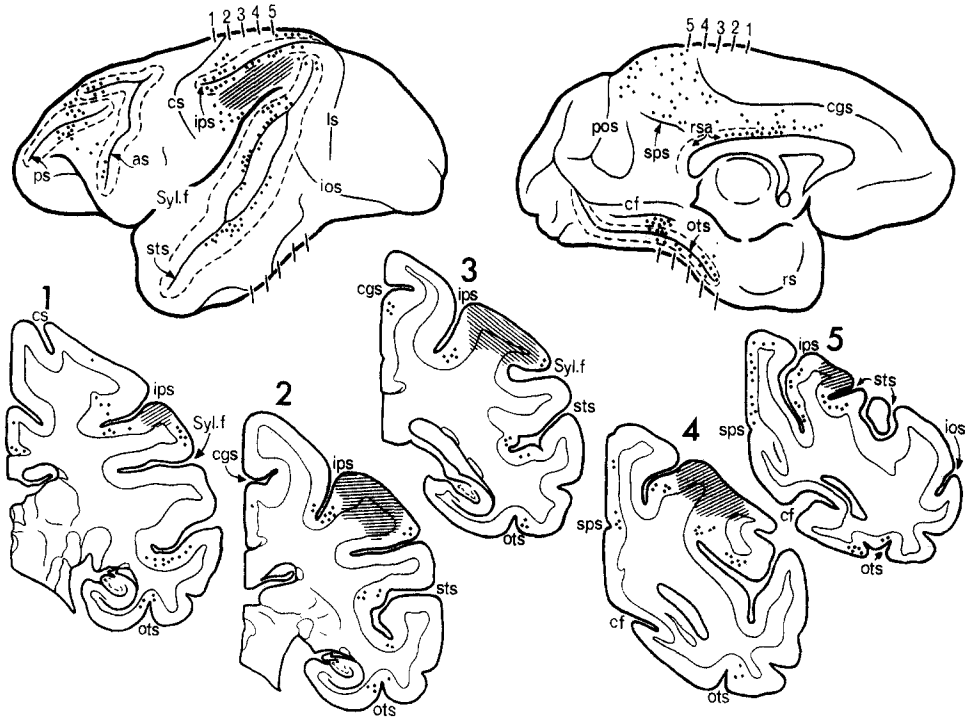

Fig. 4. Case 2. This figure depicts the topographical localization of the HRP injection (hatching) and the distribution of cortical neurons labeled with HRP (squares).

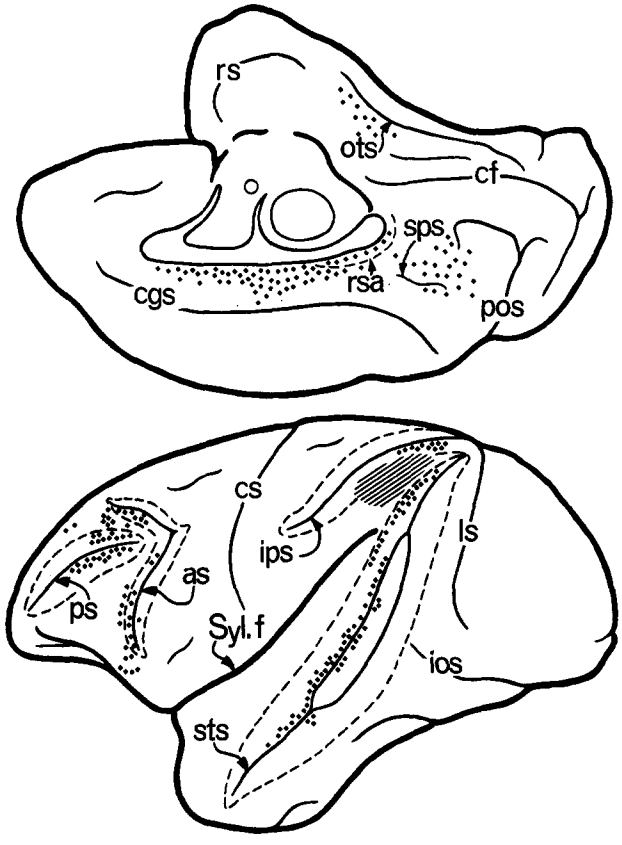

Fig. 5. Case 3. This figure depicts the topographical localization of the HRP injection (hatching) and the distribution of cortical neurons labeled with HRP (squares).

Injection sites

The injection site was identified by the presence of an intense blue color throughout the neuropil. In all 6 experiments, the injected HRP was distributed predominantly in the caudal part of the IPL (area PG of von Bonin and Bailey[4]). In three of these cases (cases 4–6), there was significant spread of the injected HRP into the dorsal portion of the peristriate belt (area OA). This spread occurred dorsal to the tip of the superior temporal sulcus and within the depths of the intraparietal sulcus. In the other three cases (1–3), the spread outside area PG was quite minor. In case 1 there was minor spread of injected HRP caudally into area OA and dorsally into area PE (Fig. 3). In case 2 the spread was almost exclusively into area PF (Fig. 4). In case 3 the injection was almost completely confined to area PG (Figs. 5, 6). In all 6 cases, area PG was extensively covered by the injected HRP. This included the full extent of PG on the dorsolateral surface of the hemisphere as well as a substantial part of its sulcal extent. Since cases 1–3 had the least spread of injected HRP outside of PG, the findings from these cases are presented in greatest detail.

The extension of injected HRP into the subcortical white matter was limited

to a 1–2 mm zone underlying the PG cortex. Since it is generally accepted that HRP is not appreciably pinocytosed into intact axons of passage[37,48], this spread into white matter is not likely to have effected our results. Damaged axons, on the other hand, will take up and transport HRP[1]. However, since the damage due to the penetration of the needle did not extend beyond 0.5 mm of subcortical white matter, it is unlikely that the results described below have been influenced by the surreptitious uptake of HRP into damaged axons of passage.

Distribution of neurons labeled with HRP

Labeled neurons were seen in many cortical and subcortical regions. In many of these areas, and especially in cortex and thalamus, 50–100 labeled neurons could be seen in a given area in one tissue section. Hence, there is little doubt that a significant projection into PG originates in these areas. In this report, only ipsilateral connections of area PG will be described.

Distribution of labeled neurons in cortex (Figs. 3–6)

Frontal lobe. Each of the 6 cases contained labeled neurons in the frontal cortex. These were situated in the banks of the caudal one-half of the principal sulcus, in the anterior bank of the arcuate sulcus and in parts of exposed periarcuate cortex. In case 3 (Fig. 6) some labeled neurons were also seen in area 12 of Walker[67]. On cytoarchitectonic grounds, the parts of the frontal lobe which consistently contained labeled cells were areas 8, 45 and 46. These observations are consistent with previous anterograde degeneration studies[29,51,53,54].

Parietal lobe. In all cases labeled neurons were observed along the caudal bank of the intraparietal sulcus and along the medial surface of the parietal cortex. Most of the labeled neurons within the intraparietal sulcus were confined to its dorsal one-third. Another area which was densely populated with labeled neurons was situated on the medial wall of the hemisphere, especially along the subparietal sulcus. The cytoarchitectonic nature of this area has not yet been clarified. While Bonin and Bailey[4] suggest that this area has the same architectonic properties as the superior parietal lobule, Brodmann[5] stresses its similarity to the type of cortex which is found in the IPL. It is possible, as Krieg has suggested[33], that a transitional type of cortex (area 31) occupies this medial part of the parietal lobe.

Another difficulty is encountered in deciding whether or not some of the labeled cells in these regions may be considered to belong to area OA. Since the caudal bank of the intraparietal sulcus as well as the caudal border of the medial parietal lobe contain zones of contiguity with area OA, this possibility cannot be excluded. However, based on the topographical localization of area OA in the rhesus monkey as well as our cytoarchitectonic observations in these cases, the contribution of OA to the total number of labeled neurons would seem to be minor.

In the two cases where the HRP injection spread into areas PE and PF, few labeled cells were also seen in the caudalmost aspect of the superior parietal lobule (cases 1 and 2), in the anterior banks of the intraparietal sulcus (case 2), in area PF (cases 1 and 2) and in area PC (case 2).

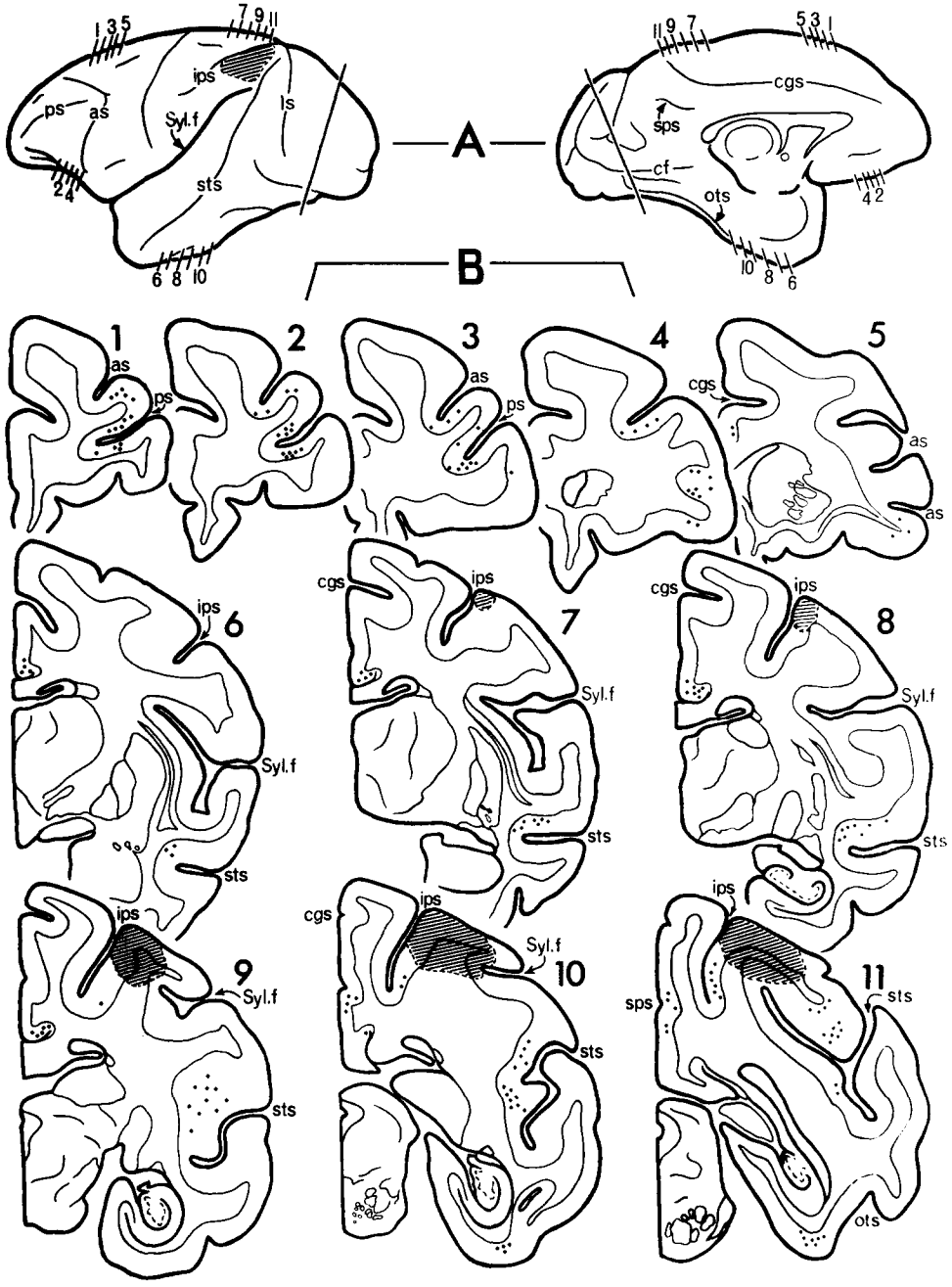

Fig. 6. Case 3. This figure illustrates the details of the HRP injection (hatching) and of the distribution of cortical neurons labeled with HRP (squares). The transverse sections are taken from the same case which is shown in Fig. 5.

Temporal lobe. In all 6 cases labeled neurons were seen along the banks of the occipitotemporal and superior temporal sulci. In the superior temporal sulcus, these neurons were predominantly encountered along two longitudinal bands on the upper bank (Fig. 6). In case 2, labeled neurons were also concentrated in the depths of the lower bank. Labeled neurons along the occipitotemporal sulcus were most consistently seen in area TF. However, some labeled neurons were observed to extend more caudally into what is a region of contiguity with area OA. This was especially accentuated in cases 4–6 which had a significant spread of the injected HRP into area OA. A few labeled neurons were also seen along the lateral bank of the occipitotemporal sulcus, in area TE.

Occipital lobe. In cases 4 and 5 with the most extensive spread of injected HRP into area OA, many labeled cells were observed in areas OA and OB along the lunate, calcarine and occipititemporal sulci. A few such neurons were also seen in case 1 where there was some spread of the injection into area OA. In cases without significant involvement of area OA by the injection, only very few labeled neurons were observed in regions which had the cytoarchitectonic properties of area OA.

Limbic lobe. In the cingulate gyrus many labeled neurons were seen in areas LC (area 23 of Brodmann) and LA (24 of Brodmann). In fact, the cingulate gyrus contained one of the heaviest concentrations of labeled neurons in most of the cases. At some levels, 40–60 labeled neurons could be seen within the cingulate gyrus in one section (Fig. 1B). Most of these cells were confined to the ventral half of the gyrus. We were also surprised to see that many labeled neurons were located within the retrosplenial area (Fig. 1A). These neurons were observed in the granular as well as the agranular parts of the retrosplenial area[65].

Summary of the cortical distribution. The cortical regions which consistently contained labeled neurons in all 6 cases are the pre- and periarcuate cortex, the caudal bank of the intraparietal sulcus, the banks of the superior temporal sulcus, the medial parietal cortex along the subparietal sulcus, cingulate cortex, the retrosplenial area and the banks of the occipitotemporal sulcus. Quite clearly, the exact pattern in the density and distribution of labeled cells varied from case to case (Figs. 3–5). In some cases, moreover, there were additional areas which contained labeled neurons. It is reasonable to assume that these variations are due to differences in the exact size and extent of the injected area. However, the verification of this assumption necessitates additional experiments with smaller injections, perhaps made by iontophoretic means.

Laminar distribution of labeled neurons in cortex

Neurons labeled with the blue HRP reaction-product were observed in virtually all cortical layers. In general, most of these belonged to the group of large and medium sized pyramidal cells of layers IIIc and V. However, different cortical areas had an individual laminar pattern of labeled neurons. For instance, the great majority of labeled neurons in area TF was confined to layers V and VI (Fig. 1C). In distinct contrast, most of the labeled neurons in the medial parietal cortex were in layer III (Fig. 2). On the other hand, labeled neurons along the principal and superior temporal sulci seemed to be evenly divided between the supra- and infra-granular

layers. It is not yet known if this pattern of lamination is a general property of a cerebral area or if this is subject to change depending on the target of the projections. Labeled neurons in layer IV were seen only in close proximity to the injection site. Although the large pyramidal neurons in layers III and V were the most visible, the blue reaction-product was also easily identified in smaller neurons.

Labeled neurons in subcortical areas

Basal forebrain and acetylcholinesterase histochemistry. The labeled neurons of the basal forebrain were predominantly seen in the nucleus basalis of the substantia innominata (Figs. 1e, 7). Some labeled neurons, perhaps aberrant members of the nucleus basalis, were also observed in the septal and lateral hypothalamic areas. The labeled neurons in the claustrum were confined to a rostrocaudal band along its ventral one-half. Similar projections from the basal forebrain to diverse cortical areas have been demonstrated previously[16,27,31,44].

The method which enables the simultaneous demonstration of HRP and acetylcholinesterase (AChE) within the same tissue section clearly showed that almost all of the HRP labeled perikarya in the nucleus basalis were also rich in AChE content. It has previously been shown that projections from the nucleus basalis to other neocortical areas are similarly AChE-rich[42,44].

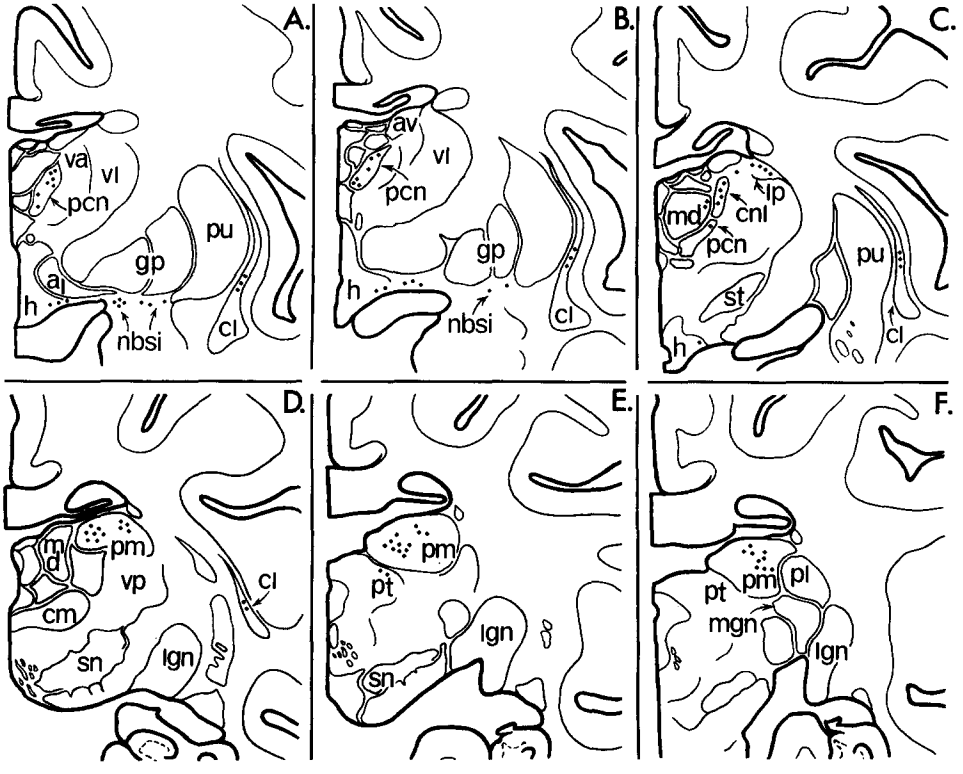

Fig. 7. Case 3. This figure depicts the distribution of basal forebrain and diencephalic neurons labeled with HRP (squares). The transverse sections are taken from the same case which is illustrated in Fig. 5.

Labeled neurons in thalamus. Two groups of thalamic nuclei contained almost all of the labeled neurons: the LP-pulvinar complex and the intralaminar nuclear group. In the LP-pulvinar group, most of the labeled neurons were confined to the medial pulvinar (Fig. 7). However, some were also observed in caudal LP and in the dorsomedial part of the lateral pulvinar nucleus. In cases 4 and 5 where there was a significant spread of the injection into OA, many labeled neurons were also seen in the inferior pulvinar nucleus. On the other hand, in case 2 where there was spread of the injection into PF, labeled neurons were also seen in pulvinar oralis. These observations are partly consistent with previous investigations[7,15,66]. The distribution of labeled neurons within the pulvinar nucleus did not follow a continuous gradient and consisted of 2–3 patches of densely packed neurons separated by areas where labeling was undetectable.

In the intralaminar group, the centralis lateralis and paracentralis nuclei contained most of the labeled neurons. With more rostral injections, as in case 2, the parafascicular nucleus also contained labeled cells. That these intralaminar nuclei project to neocortex has been shown before[28]. Occasionally, labeled neurons were also seen in the nucleus medialis dorsalis and in the magnocellular part of the medial geniculate nucleus.

Labeled neurons in brain stem. These were seen in the pretectal area, in the dorsal and medial raphe nuclei and in the nucleus locus coeruleus. The labeled neurons in the last nucleus were primarily ipsilateral to the injection but few contralateral cells also contained the label. The approximate ratio was 6 ipsilateral cells per contralateral cell. That the nucleus locus coeruleus of the monkey projects directly to neocortex has been shown previously[18].

Control case

In the one monkey which had no injection of HRP and which was processed according to the BDHC procedure, no evidence of labeled neurons was detected in any of these sites.

DISCUSSION

Connections of PG

The distribution of neurons labeled with HRP reveals that the afferents of area PG originate in diverse regions of cortex, basal forebrain, diencephalon and brain stem (Fig. 8). These sources of afferents may be classified into such categories as 'sensory association', 'limbic', and 'reticular'. Neocortical areas along the principal, arcuate, intraparietal, subparietal, superior temporal and occipitotemporal sulci where labeled cells were detected may constitute the 'sensory association' input into PG. On the other hand, projections from the basal forebrain, from cingulate cortex and from the retrosplenial area may carry predominantly 'limbic' information. Finally, the projection from intralaminar thalamic nuclei, from the pretectal region, from the nucleus locus coeruleus and from the raphe nuclei may be considered as the 'reticular' component of the afferents into PG.

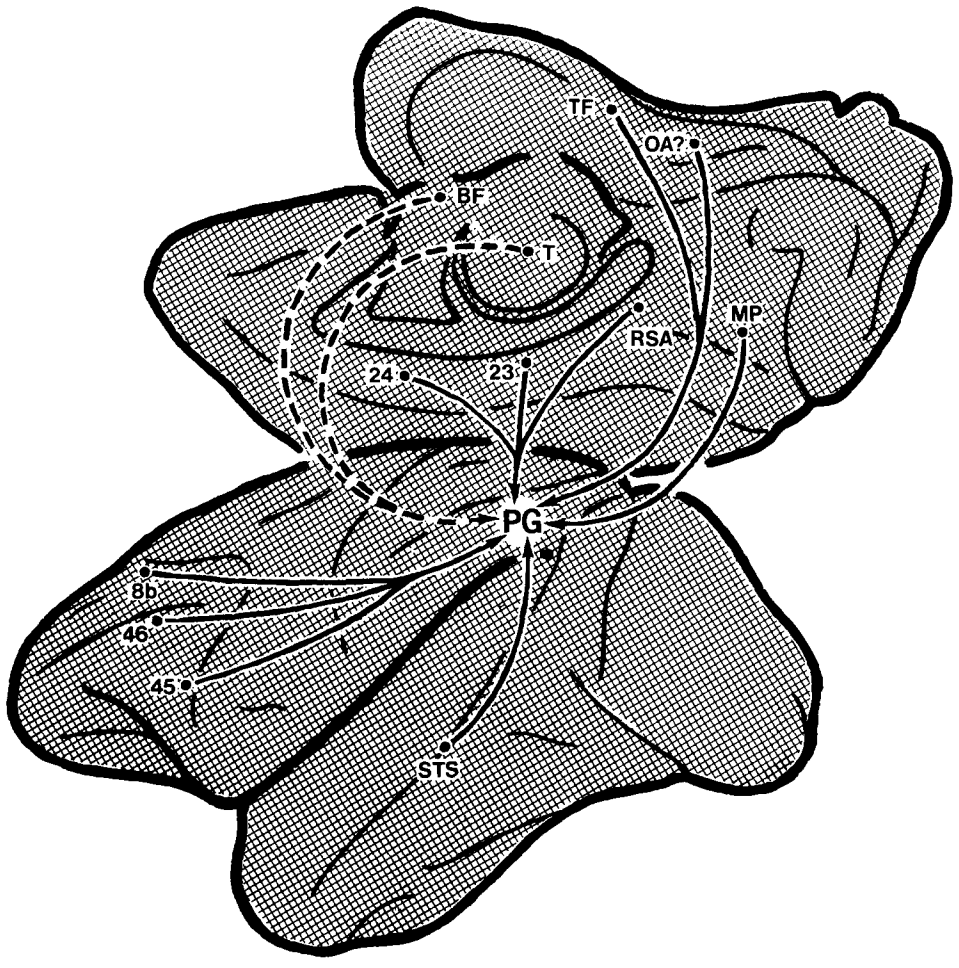

Fig. 8. This figure summarizes the various cortical and subcortical areas where labeled neurons were consistently observed following HRP injections into the caudal portion of the inferior parietal lobule (area PG).

Sensory association afferents of PG

The set of contingencies which regulates the response characteristics of units in the IPL of the monkey[25,45] suggests that these neurons may have a role in the function of attention. Furthermore, the sensory neglect which results from ablations in this area[15,17,22] would support a similar conclusion. In order to execute such a role in attention, it is reasonable to assume that the IPL receives sensory information. However, tracing the course of the sensory input into area PG (dorsal IPL) leads to a somewhat striking observation. Indeed, with the possible exception of a relatively minor contribution from areas OA and TE, none of the neocortical areas which project into PG may be characterized as an 'association' area in any single sensory modality. Therefore, in order to trace the putative and circuitous route which sensory information must take before reaching PG, it becomes necessary to consider the neural input of those areas which, in turn, project to area PG.

Since the conceptual and experimental issues concerning sensory 'association' areas have already been discussed in detail, they will not be reviewed here[9,19,29,45]. Indeed, there is consensus of opinion that a cortical region whose predominant cortical input originates in a primary sensory cortex (either koniocortical or parasensory) and which consistently yields physiological and behavioral observations confined to that modality is a bona fide 'association' area for the modality in question. Consequently, it is generally accepted that the superior parietal lobule (area PE), the superior temporal gyrus (area TA), and the circumstriate (areas OB, OA) and inferotemporal (area TE) cortices are 'association' areas in the somesthetic, auditory and visual modalities, respectively[9,29,61]. It is of considerable interest to note that none of these areas is a major source of projections into area PG in the present material. Nevertheless, each one of these association areas has been shown to project to cortical areas which, in turn, send major projections into area PG.

For instance, the part of prefrontal cortex which projects to area PG receives neural input from somatosensory association cortex in area PE[9,53], from auditory association cortex in area TA[9,29,52,53], and from the visual association regions in areas OA and TE[9,29,53]. Secondly, the caudal bank of the intraparietal sulcus receives input from area OA[29,53,57] and from PE[29]. On the other hand, a different combination of input from area PE[29,53] and from TA[52] reaches the medial parietal cortex which projects to area PG. A third combination of afferents originating in area TE[29,53,60] and TA[29,52,53,60] reaches the parts of the superior temporal sulcus where labeled neurons were seen in our experiments. Finally, the medial part of the occipitotemporal sulcus (area TF) is the recipient of projections from area OA[61].

Hence, information which originates in the immediate association areas of the three modalities is subjected to *at least* one additional relay before reaching area PG. Moreover, a different permutation of modalities seems to occur at each one of these relays: visual, somesthetic and auditory within prefrontal cortex; visual and somesthetic in the intraparietal sulcus; somesthetic and auditory in medial parietal cortex; auditory and visual within the banks of the superior temporal sulcus; visual in areas TF. It is possible, of course, that incoming sensory information from the different modalities may form crossmodal connections at these cortical sites. Furthermore, the paucity of unimodal information which has direct access to area PG is underlined by two observations. First, the possible contribution of OA and TE to the total population of labeled neurons has been a minor one when the HRP injection remains confined to area PG. Secondly, no labeled neurons were observed in the part of the superior temporal sulcus which corresponds to the region where Zeki[74] has been a direct projection from visual koniocortex.

The multisynaptic route which sensory information seems to take in order to reach area PG suggests a classification of 'sensory association' cortex into several categories. On one hand, areas PE, TA, OA, OB and TE are *unimodal* association areas which are, in all likelihood, committed to a single sensory modality. The convincing evidence in favor of this conclusion has been discussed elsewhere[9,29,61]. On the other hand, regions such as peri- and pre-arcuate cortex, the banks of the superior temporal sulcus, and perhaps others, constitute *polymodal* association areas where

crossmodal convergence among sensory modalities may occur[9,60]. In fact, there is behavioral and physiological evidence for such convergence in the periarcuate region[3,64] as well as in the cortex of the superior temporal sulcus[12]. In contrast to these *polymodal* areas which receive combinations of *unimodal* inputs, area PG receives its sensory afferents, almost exclusively, from *polymodal* cortex. Hence, area PG may constitute a subsequent stage in the processing of sensory information. On the basis of this pattern of connectivity, then, area PG may be classified as a *supramodal* association cortex. It is possible that the purpose of this successive elaboration of sensory information is to achieve a more comprehensive and, at the same time, selective representation of the sensory space. A similar pattern of processing may also exist for the modalities of taste and smell.

The conclusions reached by behavioral and physiological investigations would be consistent with the *supramodal* connectivity pattern which we show in area PG. In fact, Mountcastle et al.[45] point out that the activity in some of the IPL units was 'independent of the modality of the sensory cuing signals . . . (p. 885)'. Furthermore, the same authors state that little evidence was found for crossmodal convergence within IPL units. We suggest that this independence from modality and the lack of evidence for sensory convergence may reflect the fact that extensive crossmodal convergence has already taken place at a synaptic site which *precedes* area PG.

The input from the pulvinar nuclei into area PG may also be included in this category of 'sensory association' input. Indeed, unit recordings in the cat have demonstrated that impulses in all three modalities converge onto the same neuronal pool in the pulvinar nucleus[32].

It is not entirely clear what the architectonic homologue of the monkey's IPL is in man. If Brodmann's[5,6] parcellation is accepted, then the inferior parietal lobule of man (areas 39 and 40) has no homologue in the monkey. On the other hand, Bonin and Bailey's[4] parcellation as well as that of Krieg[33] would indicate that the IPL of the monkey is cytoarchitectonically homologous to that of man. In fact, the type of neuronal connectivity which has been described for PG in the monkey may well subserve the complex, and often supra-modal, deficits which follow IPL lesions in man[11,19,21,43].

Limbic afferents of PG

Another major source of afferents into area PG may be traced to components of the 'limbic system'. The 'limbic system' is a construct which is commonly used to denote a set of interconnected structures which have intimate, albeit multisynaptic, connections with the hypothalamus and parts of the mesencephalon. It is also generally believed that constituents of this system are implicated in the regulation of the internal milieu and in the modulation of drives and emotions[38,46,55]. In keeping with this definition, then, regions such as the cingulate cortex, the retrosplenial area and the basal forebrain where labeled neurons were observed in these experiments may be considered as components of the limbic system.

In the basal forebrain, most of these labeled neurons were located within the nucleus basalis of the substantia innominata. Physiological and anatomical evidence

would indicate that this is a region where multiple 'limbic' inputs may converge and which may have a significant function in the integration of feeding and drinking. For instance, this area receives neural inputs from the amygdala, orbitofrontal cortex, hypothalamus, olfactory bulb and pontine gustatory centers[24,47,49,59]. Furthermore, units in the substantia innominata of the monkey have been found to respond to the sight, taste or delivery of food[8,14]. Moreover, their rate of firing showed increments with increases either in the palatability of the food or in the state of hunger of the animal[8]. Hence, the input from the basal forebrain may enable neurons in the IPL to assess the actual desirability of a food object. The response characteristics of units in the IPL[25,45] would be entirely consistent with this type of anatomical connectivity.

Furthermore, the results of the present experiments have also shown that almost all of the substantia innominata cells which project to PG are rich in acetylcholinesterase (AChE). It has become quite clear that several other neocortical areas receive direct projections from basal forebrain structures and that these may also be AChE-rich[16,27,31,42,44]. It is likely that the effect of this limbic and possibly cholinergic input has different consequences depending on the nature of the cortical area within which it terminates.

A larger and somewhat more surprising source of limbic input into area PG originates in the cingulate gyrus. In all of the cases described here many labeled neurons were seen in areas LC, LA and in retrosplenial cortex. Morphological properties of parts of this complex area have recently been discussed in detail[65] and will not be reviewed here. On the basis of its connections with the anterior thalamic nuclei and the hippocampal gyrus, this region has been considered as an important component of a neural circuit which is believed to modulate emotional behavior[2,38,46,55,63,73].

Hence, this projection from retrosplenial and cingulate cortices to area PG may provide a major corticocortical pathway which establishes an interaction between *supramodal* sensory data and limbic messages. One possible role of such a connection may be to direct the attention of the organism toward motivationally relevant events. While the basal forebrain may be concerned with a limited set of simple reinforcements such as food or drink, the cingulate cortex may be involved in the more complex aspects of reinforcement and with their modification by learning. Furthermore, whereas the basal forebrain projects widely to neocortical areas, the cingulate cortex has a much more limited efferent field (unpublished data). This selectively may make the cinguloparietal projection all the more significant.

The importance of such reciprocal connections between limbic structures and sensory association neocortex has been discussed in detail with respect to their role in attention, emotion and other complex behaviors[19,38,43,46,63,68]. In fact, in 1937 Papez stated that 'radiations of emotive process from the gyrus cinguli to other regions in the cerebral cortex would add emotional colouring to psychic processes'. Although we may hesitate to endorse the exact terminology, we find ourselves in essential agreement with Papez' seminal interpretation.

Reticular afferents of PG

The inputs from the intralaminar nuclei, the nucleus locus coeruleus and the raphe nuclei are included in this group. Since these structures have been implicated in the phenomena of cortical arousal, the recruiting response and the different stages of sleep[26,30], their projections may serve to moludate the activity of area PG according to the general level of arousal. Furthermore, since fibers of the spinothalamic tract terminate in the intralaminar nuclei[40], the projections from these thalamic nuclei to area PG may serve to direct attention primarily to noxious stimuli. As in the case of projections from the basal forebrain, it is well known that efferents from intralaminar thalamic nuclei and from the nucleus locus coeruleus are also widely distributed within neocortex[18,28].

Efferents of PG

Anterograde degeneration studies have shown that area PG projects to pre- and peri-arcuate cortex, cingulate cortex, medial parietal cortex, the banks of the superior temporal sulcus, area TF and the pretectal region[9,29,34,53,61]. Hence, there is close reciprocity between the afferents and efferents of area PG. In fact, since the peri-arcuate cortex and the superior colliculus have been shown to have pivotal roles in the integration of exploratory head and eye movements[56,72], the projections from area PG to prefrontal cortex and to the pretectum may coordinate the motor sequences which are necessary for initiating exploration or for the maintenance of attention. Furthermore, the projection to cingulate cortex may establish a neural pathway for relaying sensory information into the limbic system.

The role of PG in attention

The sensory neglect which follows IPL ablations[15,17,22] and the response characteristics of units in this area[25,45] would clearly implicate this cortical area of the monkey in the process of attention. Furthermore, the anatomical connections which we have described would seem to be consistent with such a function. In specific, while the sensory association input may provide an elaborate representation of the sensory space, the limbic connections may coordinate the effective distribution of attention towards the motivationally relevant events within that sensory space. However, the IPL is not the only cerebral area which has been implicated in multimodal attention. In fact, ablations in the periarcuate region[70], in cingulate cortex[68], in the superior colliculus[62], in the lateral hypothalamus[39], and even in the mesencephalic reticular formation[69] have also caused multimodal neglect in the contralateral sensory space. Nevertheless, it is of interest that, with the possible exception of the mesencephalon, all of these regions have neural connections with the IPL. Indeed, even the mesencephalic lesion may have its effect on attention by interfering with the connections between the IPL and the pretectum or brain stem.

Furthermore, it is of interest that the three neocortical regions (periarcuate cortex, cingulate cortex, IPL) where ablations cause multimodal neglect, are reciprocally connected with each other by means of direct corticocortical connections[13,29,53]. This pattern of connectivity suggests that there may be three topographical loci concerned with the coordination of sensory attention. On one hand, a stage of *afferent*

integration may occur at the IPL where a *supramodal* representation of the sensory space is formed. On the other hand, the cingulate cortex may constitute a locus for *limbic integration* where the motivational relevance of ongoing events is assessed. Thirdly, periarcuate cortex may subserve a role of *efferent integration* for the initiation or inhibition of attentive behavior. The efficient interaction among these three stages of integration may be indispensable for the effective execution of attention.

Methodology of HRP neurohistochemistry

A comparison of matching tissue sections reacted with diaminobenzidine (DAB) and benzidine dihydrochloride (BDHC) revealed striking differences. As noted previously, the BDHC method yields superior visibility for light microscopic investigations. Secondly, the BDHC method was found more sensitive and less prone to the artifactual deposition of reaction-product. In fact, in some cortical areas where a representative DAB procedure revealed virtually no labeled neurons, many labeled neurons were observed in matching sections processed with BDHC. Despite the persistence of a quantitative superiority in favor of BDHC, such critical differences were not observed in subcortical structures.

This difference from one method to another becomes less surprising if the dynamic nature of HRP neurohistochemistry is considered. In fact, there are many critical variables which determine the degree of success in an HRP neurohistochemical experiment[35,41]. These may be divided into two major groups. Variables in the first group determine how effectively HRP is transported into the perikarya of neurons which project into the injected site. On the other hand, variables in the second group determine how effectively the transported HRP is made visible. The superiority of the BDHC method is related to the variables in this second group. The specific factors which determine this superiority have been discussed in detail[41].

Hence, as the processes which govern the enzymatic visualization of transported HRP are better understood, it is becoming evident that the choice of chromogen and of incubation parameters influence the effectiveness of an HRP neurohistochemical experiment. Until proper experimentation reveals a more effective method, furthermore, this BDHC method is our procedure of choice for tracing the retrograde intraaxonal transport of HRP at the level of light microscopy.

LIST OF ABBREVIATIONS

AChE = acetylcholinesterase
al = ansa lenticularis
as = arcuate sulcus
av = anterior ventral thalamic nucleus
BDHC = benzidine dihydrochloride
BF = basal forebrain
cf = calcarine fissure
cgs = cingulate sulcus
cl = claustrum
cm = central median thalamic nucleus
cnl = centralis lateralis thalamic nucleus
cs = central sulcus
DAB = diaminobenzidine
gp = globus pallidus
h = hypothalamus
HRP = horseradish peroxidase
IPL = inferior parietal lobule
ips = intraparietal sulcus
ios = inferior occipital sulcus
lgn = lateral geniculate thalamic nucleus
lp = lateral posterior thalamic nucleus
ls = lunate sulcus
md = medial dorsal thalamic nucleus
mgn = medial geniculate thalamic nucleus
MP = medial parietal area
nbsi = nucleus basalis of the substantia innominata
ots = occipitotemporal sulcus

pcn	= paracentralis thalamic nucleus	sn	= substantia nigra
pl	= lateral pulvinar thalamic nucleus	sps	= subparietal sulcus
pm	= medial pulvinar thalamic nucleus	st	= subthalamic nucleus
pos	= parieto-occipital sulcus	sts	= superior temporal sulcus
ps	= principal sulcus	Syl. f	= sylvian fissure
pt	= pretectal area	T	= thalamus
pu	= putamen	va	= ventral anterior thalamic nucleus
rs	= rhinal sulcus	vl	= ventral lateral thalamic nucleus
rsa	= retrosplenial area	vp	= ventral posterior thalamic nucleus

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Recently, a 3,3′,5,5′-tetramethylbenzidine (TMB) method has been described for HRP neurohistochemistry (M.-M. Mesulam and D. L. Rosene, Differential sensitivity between blue and brown reaction procedures for HRP neurohistochemistry, *Neurosci. Lett.*, 5 (1977) 7–14). This TMB method also yields a blue reaction-product and shares the advantages of the BDHC method, while having less of a carcinogenic potential.

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