standing of the biochemical mechanisms of ischemic cerebrovascular disease and perhaps lead to more effective preventative treatment.

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5. Tubocurarine chloride injection, U.S.P. (20 units per milliliter, E. R. Squibb, Princeton, N.J.) was injected intramuscularly in a dose of 10 units.
6. Sodium heparin injection, U.S.P. (1000 units per milliliter, Upjohn, Kalamazoo, Mich.) was injected into the right external jugular vein in a dose of 100 units.
7. Liberal infiltration of the anterior cervical region was carried out with xylocaine HCl, 1 percent (Lidocaine, Astra, Worcester, Mass.).
8. A piece of PE-10 tubing (Clay-Adams, Parsippany, N.J.) was inserted into the common carotid artery, and its tip was positioned at the bifurcation of the carotid.
9. Arachidonic acid (>99 percent pure, Sigma, St. Louis, Mo.) was dissolved in a nitrogen atmosphere at 0°C in a clear physiologic-saline solution containing 65.6 m*M* Na_2CO_3 and 10 percent ethanol. Aliquots of the resulting 33 m*M* sodium arachidonate solution were pipetted into glass ampules, frozen in liquid nitrogen, and sealed under vacuum. All ampules were stored in the dark at — 60°C until use. Subsequent dilutions were made with sterile physiologic saline just prior to use.
10. Several rats received carotid injections of arachidonate under ether anesthesia and were allowed to awaken. The details of the unusual clinical picture of irreversible neurologic deficits that resulted are in preparation for publication.
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12. The brain and other organs were removed immediately after death and fixed in 10 percent neutral formalin. The paraffin blocks were cut at 5 μm and stained with hematoxylin and eosin and with periodic acid–Schiff reagent.
13. Small blocks of cerebral cortex were excised from barbiturate-anesthetized rats 30 seconds after injection of the arachidonate solution. The tissue was fixed by immersion in 2 percent glutaraldehyde in 0.1*M* cacodylate buffered to *p*H 7.3, post-fixed in osmium tetroxide, dehydrated in alcohol, and embedded in epoxy. Sections were cut 0.8 μm in thickness and stained with toluidine blue.
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15. Supported by PHS training grant 05120 and a research career development award (NS 28155) to N.H.B. We thank Dr. L. Adelman and Mrs. M. Allietta for assistance in pathologic examination of the tissue specimens.

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Basal Forebrain and Hypothalamic Connections to Frontal and Parietal Cortex in the Rhesus Monkey

Abstract. *Horseradish peroxidase was injected in different parts of the frontal and parietal cortex in 17 rhesus monkeys. In all cases the enzyme was transported retrogradely to neurons in the substantia innominata and hypothalamus as well as in the thalamus. These new findings demonstrate that these cortical areas receive direct afferent fibers from limbic basal forebrain areas concerned with emotion and motivation.*

As part of the analysis of the motor system of the brain, an attempt was made to determine in the monkey the precise location of the subcortical cell populations which send their fibers to the different parts of the frontal lobe. For this purpose the retrograde transport of horseradish peroxidase (HRP) (*1*, *1a*) from fiber terminals to parent cell body was utilized, since with this technique cells of origin of the subcortical afferents to restricted cortical areas can be demonstrated very effectively (*1a*, *2*). The findings in this study showed that the afferents to the frontal and parietal lobes are not exclusively derived from thalamic cell groups but also come from the substantia innominata and the hypothalamus, thus linking regions involved in the control of mood and motivation to neocortical areas guiding somatic motor and sensory activities. Anatomical evidence for such a link between these functionally different brain structures has heretofore been rather elusive.

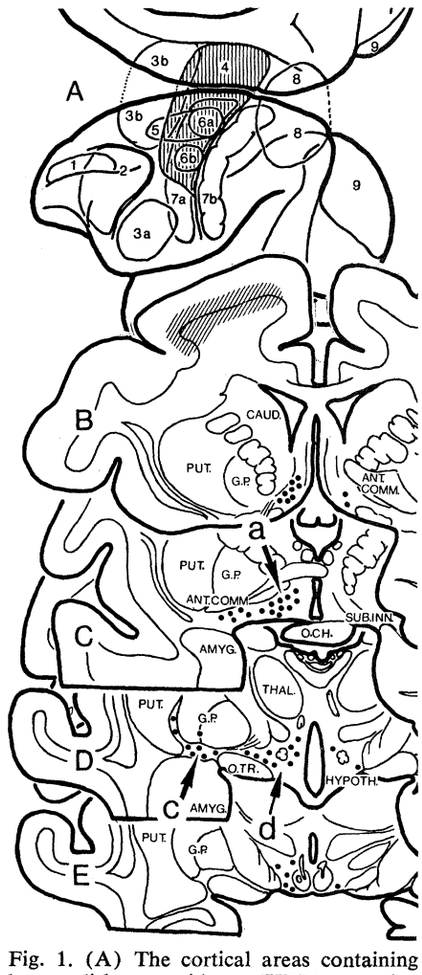

Fig. 1. (A) The cortical areas containing horseradish peroxidase (HRP) reaction products after injection of enzyme in the different lobes of the cases discussed in the text. In cases 3, 6, and 7, injections were made in both the left (*a*) and right (*b*) hemispheres. (B–E) The distribution of HRP-positive neurons in basal forebrain areas of case 4, that is, in the substantia innominata, especially the nucleus basalis, in the medullary laminae of the globus pallidus, and in the hypothalamus.

In 15 rhesus monkeys 6 to 25 closely spaced injections of 0.6 μl of 10 percent HRP (Sigma VI) in distilled water were made in different parts of the precentral gyrus and rostrally adjoining frontal areas, either unilaterally or bilaterally. In three other monkeys, the enzyme was injected in the postcentral gyrus, parietal lobules, and occipital lobe, respectively. In one control animal 30 injections of 0.6 μl of 0.0075 percent saline (approximately the same molarity as the 10 percent HRP) were made in the precentral gyrus. After 3 days the animals were anesthetized and perfused with 6 percent dextran followed by a 0.5 percent paraformaldehyde–2.5 percent glutaraldehyde mixture. The brains were kept in cacodylate buffer with 30 percent sucrose for 3 days, and cut transversally in 40-μm frozen sections which were incubated according to the method of Graham and Karnovsky (*1*), dehydrated, and covered. Some were lightly counterstained with cresyl violet. The material was studied with the microscope under bright-field and dark-field illumination.

In the control animal no retrogradely labeled HRP-positive neurons were found (Fig. 2B). In other animals HRP-positive neurons were present in the thalamus but also in the substantia innominata and hypothalamus, which will be referred to as basal forebrain areas. In some cases labeled neurons

appeared also in the claustrum. In the six animals (cases 1, 2, 4, 5, 8, and 9 of Fig. 1) with unilateral injections, the labeled neurons were present virtually exclusively on that side, whereas in cases of bilateral injection they appeared on both sides.

After precentral gyrus injections, the HRP-positive neurons in the thalamus were concentrated in the caudal part of nucleus ventralis lateralis (VL), and some were present in nucleus centralis lateralis and in caudal centre median. After injections more rostrally in the frontal lobe (for example, cases 2 and 3 of Fig. 1), the labeled neurons were concentrated more rostrally and medially in the thalamus, that is, in the rostromedial portion of the VL nucleus, in the ventralis anterior nucleus, and in the lateral part of the mediodorsal nucleus.

After injections of HRP in the precentral gyrus (case 4 of Fig. 1), the labeled neurons in the basal forebrain areas were distributed as follows. Immediately rostral to the anterior commissure a group of labeled neurons was located at the foot of the septum (Fig. 1B and 2A), mainly ipsilaterally. Some of them probably belonged to the nucleus of the diagonal band of Broca, but others seemed to be located more laterally. At the level of the anterior commissure (Fig. 1C) this population of HRP-positive neurons extended laterally through the substantia innominata, in the area of the nucleus basalis (*3*). Caudal to the optic chiasm labeled neurons continued to be present in the nucleus basalis, which at this level is located laterally immediately ventral to the globus pallidus (Fig. 1, D and E, and Fig. 2C). A few such neurons were present also in the internal and external medullary laminae of the globus pallidus, which have been reported to contain cells of the nucleus basalis (*3*). HRP-positive neurons appeared also in the lateral hypothalamus at these levels (Fig. 1, D and E), and some were located in the area around the fornix and dorsally in the medial hypothalamus (Fig. 1, D and E, and Fig. 2D).

HRP-positive neurons also appeared in the basal forebrain areas when the enzyme was injected in restricted parts of the precentral gyrus, as in cases 5 and 6 of Fig. 1. These neurons showed the same distribution as in case 4, but were less numerous. Labeled neurons were found bilaterally in the basal forebrain areas when the enzyme was injected in the area above the arcuate sulcus in one hemisphere and below it in the other, as in case 3 of Fig. 1. They were found also in case 2 of Fig. 1 ipsilateral to an HRP injection in the arcuate gyrus and in smaller numbers in case 1 of Fig. 1 with injections in the rostral part of the upper part of the upper bank of the principal sulcus.

In order to determine whether HRP was also transported from cortical areas behind the central sulcus to the basal forebrain areas, the enzyme was injected in these cortical areas in three monkeys (cases 7, 8, and 9 of Fig. 1). In case 7, injections were placed in the postcentral gyrus on one side and in the precentral gyrus on the other, while in case 8 of Fig. 1 they were made in the superior and inferior parietal lobules on one side. In these two animals likewise, HRP-positive neurons were present in the basal forebrain areas, bilaterally in case 7 (Fig. 2D) and almost exclusively ipsilaterally in case 8. However, in case 9 of Fig. 1 with injections in one occipital lobe very few labeled neurons appeared in the rostral part of the nucleus basalis (levels B and C in Fig. 1). Yet, some were present in the caudal part of the nucleus and in the internal and external medullary laminae of the globus pallidus (level D of Fig. 1), and a few were found in the hypothalamus.

The fact that in 17 monkeys HRP injections in the frontal, postcentral, and parietal cortex consistently resulted in retrograde transport of the enzyme to cells in the nucleus basalis of the substantia innominata and in the hypothalamus indicates that neurons in these basal forebrain areas send axons to the neocortex of these lobes. Recent electrophysiological findings had suggested the possible existence of such direct connections (*4*), but to our knowledge such connections had not been demonstrated anatomically.

The direct fiber connections from the basal forebrain areas to the frontal and parietal cortex are comparable in some respects to the ascending monoaminergic pathways (*5*) which also lead directly from cell groups in the brainstem to the cortex. These monoaminergic pathways in addition may be connected with the projection system from the basal forebrain areas, since the monoaminergic fibers on their way to the cortex in part traverse the lateral hypothalamus and the substantia innominata (*5*).

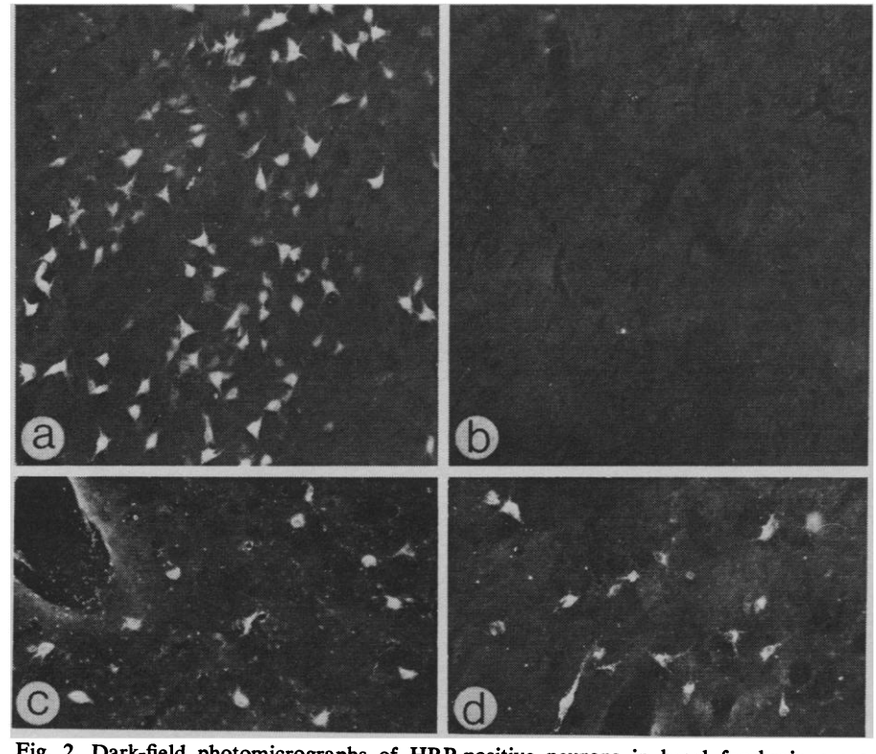

Fig. 2. Dark-field photomicrographs of HRP-positive neurons in basal forebrain areas after injection of the enzyme in frontal and parietal cortex. (a) Concentration of HRP-positive neurons (×56) in case 4 in medial part of substantia innominata (area labeled *a* in Fig. 1C). (b) The same area (×56) in control animal with saline injected in precentral gyrus. (c) HRP-positive neurons (×56) in case 4 in caudal part of nucleus basalis after light counterstaining with cresyl violet (area labeled *c* in Fig. 1D). (d) HRP-positive neurons (×61) in case 8 in lateral hypothalamus (area labeled *d* in Fig. 1D).

The substantia innominata and the lateral hypothalamus receive fiber connections from the mesencephalic reticular formation and paramedial limbic areas as well as from the amygdala (*3*). The HRP-positive neurons in the basal forebrain areas appear, therefore, to be located at the crossroads of limbic brainstem pathways. The activity of the limbic system has been shown to be related to motivational and emotional states. For example, stimulation of basal forebrain areas and hypothalamus may elicit sleep, food intake, and sexual activity (*6*), and the activity of neurons in the substantia innominata and the medullary laminae of the globus pallidus has been found in operant conditioning experiments to be related to the delivery of a fruit juice reward (*7*). In addition, lesions of the lateral hypothalamus have been shown to result in contralateral sensory inattention (*8*).

The present findings make it likely that the behavioral phenomena elicited by stimulation of limbic basal forebrain areas may be brought about not only by way of descending pathways to the brainstem as suggested by Nauta's classic anatomical findings (*3*) but also by way of the direct connections to the cerebral cortex demonstrated in the present study. Moreover, the latter connections may provide a channel by which the basal forebrain areas can influence directly the precentral motor cortex and cortical sensory areas in accordance with the motivational and emotional state of the organism.

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Symbolic Matching by Pigeons: Rate of Learning Complex Discriminations Predicted from Simple Discriminations

Abstract. *Pigeons had no greater difficulty learning a complex discrimination involving arbitrary interrelations among stimuli (symbolic matching) than one involving interrelations based on stimulus similarity (matching-to-sample). The relative rates of acquisition of matching and symbolic matching may be accounted for by the discriminability between sample stimuli* **and** *between comparison stimuli, with the former playing the more important role.*

Cumming and Berryman (*1*) reported that pigeons readily learn to select, from among comparison colors, that hue which is identical to a sample color. Their procedure for establishing matching-to-sample performance is as follows. A naive pigeon, reduced to 80 percent of its normal weight, is placed in a chamber with three response keys on one wall. When a sample is presented on the center key, a single peck at this sample turns on the remaining keys. Now three stimuli are present, the sample and two comparison stimuli, one of which is identical to the sample. If the bird pecks at the comparison that matches the sample, it is given access to grain for 3 seconds. A peck at the odd key turns off all lights in the chamber for 3 seconds. Trials are separated by a 15-second interval.

Using a variant of this procedure, Eckerman trained pigeons in a symbolic matching task (*2*). The comparison stimuli were vertical or horizontal lines, but the sample stimuli were colors. When the sample was wavelength 506 nm, pigeons were rewarded with food for pecking the horizontal line, but when the sample was wavelength

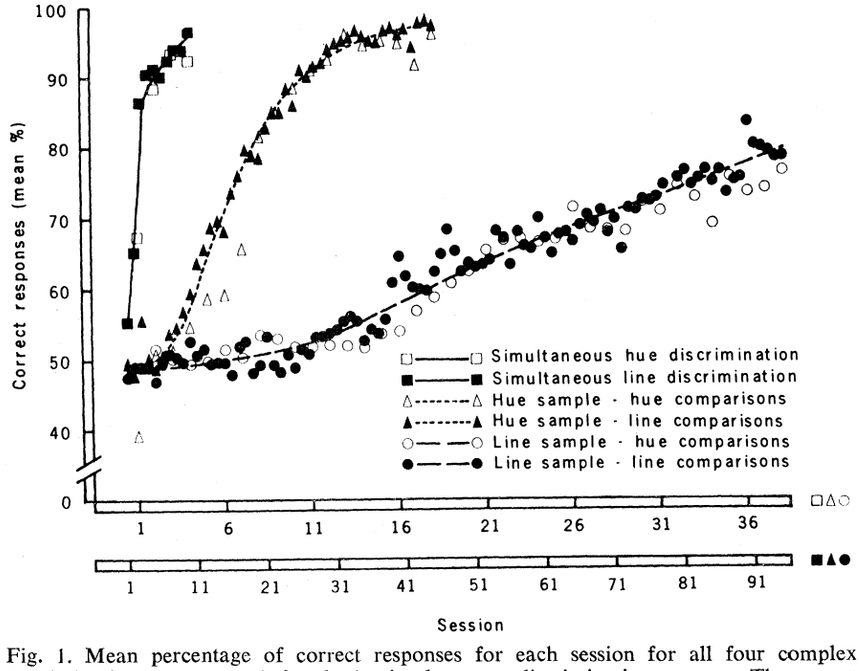

Fig. 1. Mean percentage of correct responses for each session for all four complex discrimination groups and for both simultaneous discrimination groups. The upper abscissa has been used for all discriminations involving colors on the side keys (comparison stimuli). The lower abscissa has been used for all procedures using lines on the side keys. One session on the upper abscissa is equal to 2.5 sessions on the lower abscissa.