nermost annuli 0.8 log unit brighter and 0.8 log unit dimmer than the outermost annuli.

As a further test of the prediction illustrated in Fig. 2, we measured threshold elevations for two additional test rectangle widths, namely, 0.25° and 1.0°, for three of our four subjects. Figure 3E shows how the antiphase threshold elevation curves progressively broadened as the width of the test rectangle increased from 0.25° to 1.0°.

We conclude that visual sensitivity to the location of a flow pattern's focus could be mediated by channels that respond to changes in the size of small objects. The relative activities of these changing-size channels might be one basis on which the brain computes the direction in which the head moves with respect to the external world (*11, 12*).

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3. J. J. Gibson, *The Perception of the Visual World* (Houghton Mifflin, Boston, 1950), pp. 117–144.
4. If some part of a subject's ability to use flow patterns to guide locomotion depends on neural development, and if this neural development depends on early experience in visually guided locomotion, a major increase in visual sensitivity to flow patterns might not occur until the time an infant starts to crawl alone. Furthermore, adults who had been unable to travel normally under their own volition early in life might, consequently, have abnormal responses to flow patterns so that their ability to guide their locomotion by retinal flow patterns might be impaired. This discussion amounts to a special case of the more general proposal of R. Held and A. Hein [*J. Comp. Physiol. Psychol.* **56**, 872 (1968); *Sci. Am.* **213**, 84 (November 1965)].
5. D. Regan and K. I. Beverley, *Vision Res.* **18**, 415 (1978); *ibid.*, p. 209; ——— and M. Cynader, *Proc. R. Soc. London Ser. B*, in press.
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8. Receptive field measurements have been reported (*7*).
9. We chose oscillatory stimulation for test rectangles (and therefore for flow pattern) because the chief evidence for the existence of changing-size channels was obtained with stimulus rectangles whose edges oscillated either in phase or in antiphase (*6*). This enabled us to show more clearly that selective adaptation to antiphase (changing-size) stimuli could not be explained in terms of the classical motion channel since the movements of the rectangle's edges were identical for in-phase and antiphase stimuli: the only difference was in the relationship between the motion of opposite edges. We could not have used this argument had we used asymmetric (ramping) movements.
10. For the 0.5° test rectangle, preadaptation sensitivity to changing size at 1 Hz was 1.6, 0.7, 2.8, and 1.5 minutes of arc per second (central foveal stimulation); peak threshold elevations (Fig. 3C) were 94, 250, 202, and 80 percent; and half-widths of curves (Fig. 3C) were 12, 17, 35, and 14 minutes of arc for subjects K.B., J.B., A.G., and D.R., respectively. If visual sensitivity to flow patterns is important in landing aircraft and in automobile driving, and if this visual capacity proves to be relatively uncorrelated with the results of standard visual tests, there may be flying and driving tasks for which tests of sensitivity to flow patterns or to changing size might profitably be added to present screening tests.
11. Our finding that changing-size channels are not sensitive to pairs of edges more than about 1.5° apart make sense in the light of our proposal that a major function of changing-size channels might be to provide a basis for judging the location of a flow pattern's focus, since changing-size channels sensitive to narrow objects would signal the location of the focus more precisely than those sensitive to wide objects. D. Regan and K. I. Beverley, *Vision Res.*, in press.
12. Since the radial velocity in our flow pattern did not depend on the distance from the focus, our stimulus differed from a real-world flow pattern. In a real-world flow pattern, the angular velocity of flow for an object point located along a direction $\theta°$ from the point toward which the eye is moving is proportional to $(\theta v/D)$, where D is the distance between the eye and the object point and v is the linear velocity of locomotion.
13. Threshold elevations were calculated as follows:

$$TE = \frac{T_a - T_b}{T_b}$$

where T_a was oscillation threshold after adaptation and T_b was oscillation threshold before adaptation.
14. Photograph (Fig. 1) by G. Castle, Dalhousie University. We thank J. Raymond, M. Cynader, A. Ginsburg, L. Harris, and W. K. Honig for their critical comments and N. Beattie for assistance in preparing this report. K.I.B. was supported by National Research Council of Canada grant A-0323 to D.R. Sponsored by the U.S. Air Force Office of Scientific Research, Air Force Systems Command under grant AFOSR-78-3711.

21 November 1978

Noradrenergic Innervation of Cerebral Cortex: Widespread Effects of Local Cortical Lesions

Abstract. *The trajectory of the intracortical noradrenergic fibers has been characterized by histochemical analysis following the production of cortical lesions in the rat. A large group of noradrenergic fibers enters the cortex at the frontal pole and proceeds caudally through the deep layers of dorsolateral cortex. Branches arise from these longitudinally directed fibers and form a uniform pattern of innervation throughout lateral cortex. Because these fibers travel long distances rostrocaudally within the gray matter, a large area of cortex can be deprived of noradrenergic innervation by a relatively small lesion of frontal cortex. The medial and lateral cortex can be selectively and differentially denervated of noradrenergic fibers, and there is a medial to lateral topographic relationship between deep longitudinally running fibers and overlying cortex.*

The ascending noradrenergic (NA) projection from the locus coeruleus appears to be the most divergent system in the brain, originating from a few thousand cells in the pons and innervating a large portion of the diencephalon and the entire cerebral cortex. Predictably, the projection does not mediate modality-specific sensory information but has been implicated in more general functions such as attention, mood, and vigilance (*1*). To achieve a better understanding of the role played by the coeruleo-cortical system in cortical circuitry, we have studied the morphological organization of the terminal and preterminal NA axons within the cortex of the rat. Our previous observations (*2*) indicate that the coeruleo-cortical projection is geometrically orderly throughout the lateral neocortex and that its organization differs considerably from that of other cortical afferents. Two noteworthy features of the NA innervation are the high density of fibers throughout all cortical layers and the predominantly tangential orientation of axons within the cortical gray matter. We now offer experimental data that further clarify the intracortical route of the NA fibers and that demonstrate the tangential organization of this major cortical afferent.

Throughout all areas of the lateral neocortex, a qualitatively uniform pattern of NA innervation has been found (*2*) through the use of immunocytochemical staining with antibodies directed against dopamine-β-hydroxylase (DBH) (*3*). The NA fibers in layer VI are largely oriented in the anteroposterior direction, and they form a continuous, intracortical sheet of longitudinal fibers overlying the white matter. Although tangential fibers are also seen in layers IV and V, the prevalence of short, tortuous axon segments suggests that an NA terminal field is present in these layers. Layers III and II are traversed by radially oriented axons with minimal branching, whereas layer I contains numerous tangential fibers with both anteroposterior and mediolateral orientations.

The pattern of NA innervation in the medial (cingulate) cortex differs from that of the lateral cortex. Within the medial cortex, striking differences exist between the anterior cingulate and the retrosplenial regions (*4*). The anterior cingulate cortex has a low density of NA fibers, particularly in layers II and III, in contrast to the retrosplenial cortex, which has an extremely high density of NA innervation, most evident in the middle layers, where there appears to be an NA terminal field similar to that in layer IV of lateral cortex.

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Despite the regional variations in the branching patterns, all areas of neocortex have a prominent band of tangential fibers running through the gray matter in the anteroposterior direction. Given the presence of this dense sheet of NA axons within layer VI of medial and lateral cortex and the paucity of NA fibers in the subcortical white matter, we hypothesized that the longitudinal layer VI fibers form the principle intracortical NA pathway forming "trunk lines" which, via local branches, innervate the cortex through which they pass.

This hypothesis has been difficult to reconcile with the well-established notion that NA fibers enter the cortex via either of two discrete pathways: a medial path through the cingulum bundle and a lateral projection that leaves the medial forebrain bundle and proceeds laterally to enter the external capsule (*5*). The principle NA pathway has been thought to be through the cingulum bundle as described by Ungerstedt (*5*). In his formulation, NA axons from the locus coeruleus ascend through the septal nuclei and proceed dorsally around the genu of the corpus callosum; they enter the cingulum bundle and run caudally, giving off laterally directed branches that innervate most of the neocortex. If that formulation were correct, then one would expect to see laterally directed NA axons in dorsolateral cortex, whereas we have observed in coronal, parasagittal, and tangential sections of lateral cortex that the fibers are primarily directed longitudinally.

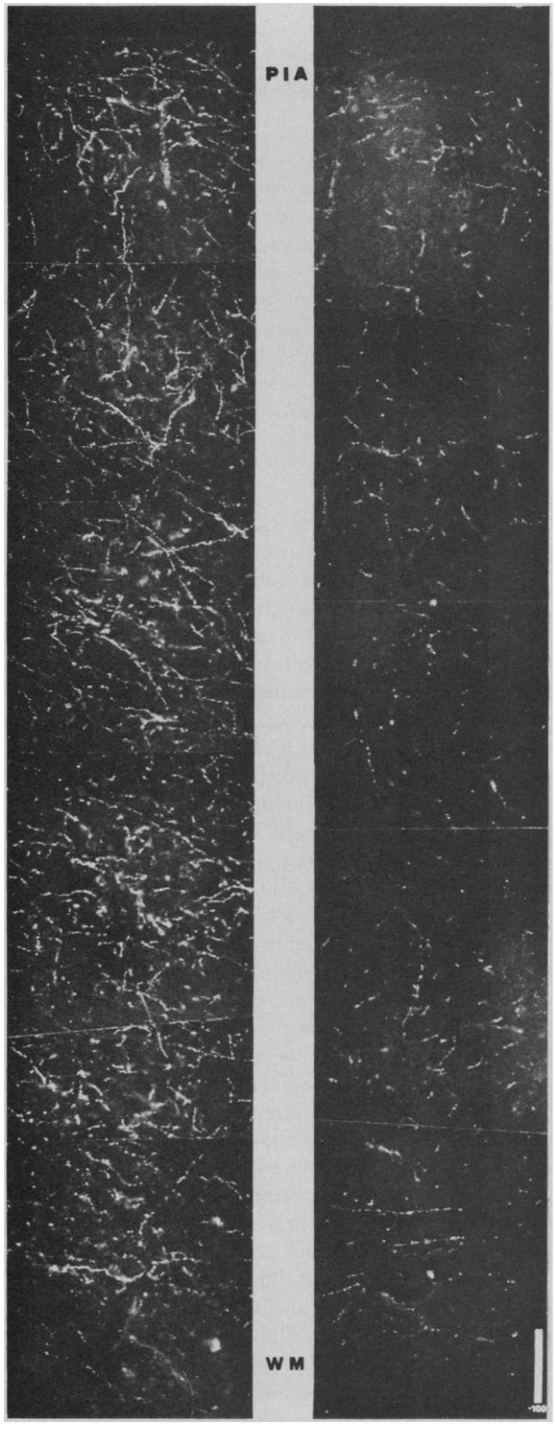

Fig. 1. Photomontages of DBH-positive fibers in the primary somatosensory cortex of the control (left) and lesioned (right) hemispheres (sagittal sections). The lesion was a coronal incision of the dorsolateral cortex from the pia to the white matter (*WM*), placed several millimeters rostral to the area shown. Note the marked decrease in the density of NA fibers on the lesioned side. The photomontages extend from the pia to the white matter (bar, 100 μm).

In order to determine the degree to which branches from the cingulum bundle innervate lateral or medial cortex, we initially made three intracortical lesions. The lesions were unilateral, and in all cases the NA innervation of the lesioned hemisphere was compared with that in the unlesioned hemisphere and in control (unoperated) rats (*6*). The first lesion was a discrete parasagittal knife-cut from the pia to the white matter in dorsal cortex lateral to the cingulum bundle. This lesion would be expected to sever any laterally directed branches arising from the cingulum bundle. After the animals had survived for 2 weeks, the NA innervation of cortex lateral to the incision appeared normal, and there was no significant decrease in the density of NA axons.

Next, we transected the cingulum bundle caudal to the genu of the corpus callosum. This lesion should interrupt all NA fibers traveling within or immediately dorsal to the cingulum bundle. The density and pattern of NA innervation in both the medial and lateral cortex was essentially normal; however, there was a moderate decrease in the density of NA fibers in the strip of cortex immediately dorsal to the cingulum bundle, caudal to the lesion.

The third lesion was a coronal incision of medial cortex, slightly caudal to the genu of the corpus callosum, that extended from the midline to the cingulum bundle, thereby transecting the supracallosal stria and the cortex immediately dorsal to it. This lesion resulted in a marked reduction in the number of longitudinally oriented NA fibers and in the density of NA innervation throughout the cingulate cortex caudal to the lesion, whereas the dorsal and lateral cortical regions were unaffected.

The results of the preceding lesion experiments demonstrate that dorsolateral cortex is not innervated to a significant degree by fibers arising from medial cortex or the cingulum bundle. The NA fi-

bers within the cingulum bundle innervate only the band of dorsal cortex overlying the cingulum bundle. Moreover, the cingulate cortex itself is innervated by NA fibers running longitudinally in and above the supracallosal stria and medial to the cingulum bundle.

The innervation of lateral cortex is thus independent of fibers running in the cingulum bundle or in the medial cortex. Since we, like Lindvall and Björklund (5), were unable to visualize a significant contribution of NA fibers to the cortex via a lateral pathway, we hypothesized that the lateral cortex is innervated by intrinsic NA fibers that enter the cortex in the frontal pole and proceed caudally within the dorsolateral cortex. Two additional unilateral lesions of the dorsolateral cortex were made in order to verify this hypothesis.

A coronal incision of the dorsolateral cortex (4 to 5 mm long) extending from the pia to the white matter was placed at a rostrocaudal level approximately 1 mm behind the genu of the corpus callosum. The cingulum bundle was not damaged, as confirmed histochemically. This lesion resulted in a marked decrease of NA innervation caudal to the cut (Fig. 1) in a wedge-shaped area of cortex extending from the lesion to the occipital cortex. The frontal cortex rostral to the lesion was unaffected, as were the medial and far lateral regions of cortex.

Finally, a dorsolateral frontal decortication was performed by aspirating gray matter of the frontal pole back to the rostral tip of the white matter. The medial cortex was undisturbed, and the lesion was restricted to the area rostral to the genu of the corpus callosum such that NA fibers ascending medially around the genu were spared. After this lesion was made, the density of NA fibers throughout all layers of dorsal and lateral cortex decreased markedly (Fig. 2) as far caudally as the occipital pole, where some fibers remained. The medial and perirhinal cortex were the only cortical areas not affected.

These lesion studies demonstrate that

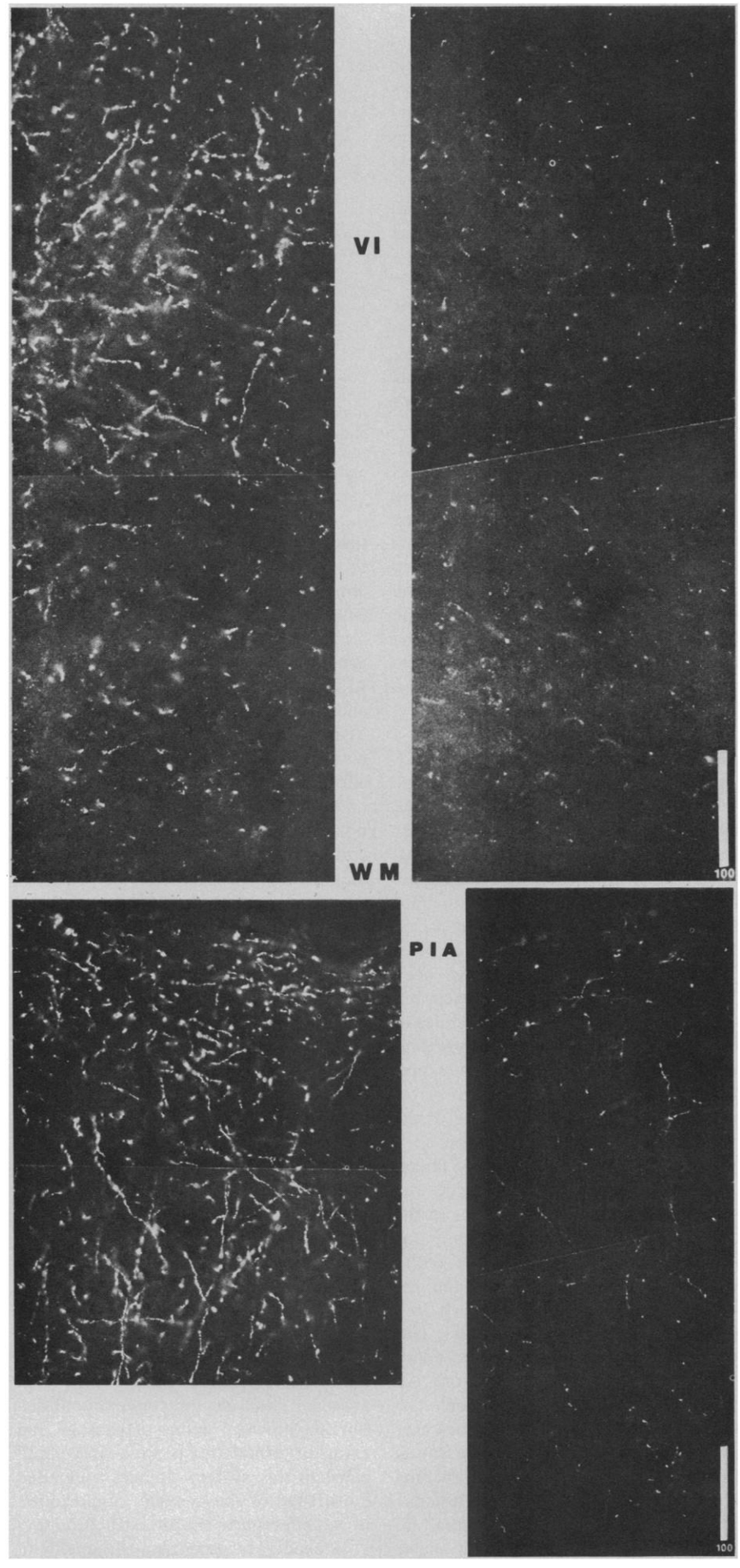

Fig. 2. The effect of frontal decortication on NA innervation of lateral neocortex. Photomontages of DBH-positive fibers in primary somatosensory cortex after unilateral frontal decortication (coronal sections; bar, 100 μm; left, control side; right, lesioned side). (Top) Layer VI. (Bottom) Layers I through III. The NA innervation density and pattern on the control side is indistinguishable from that seen in a normal animal. The few remaining fibers on the lesioned side may have reached the cortex via any of the alternate routes that have been proposed (5).

the NA innervation reaches most areas of neocortex primarily by tangential, longitudinal axons which run from rostral to caudal. A medial to lateral topographic relationship exists between deep fibers and the overlying cortex. The medial and lateral cortex are innervated by different sets of NA fibers and can be selectively and differentially denervated of NA axons. In coronal sections, both sets of longitudinally directed fibers can be seen as crosscut axons in deep cortex forming a uniform band, which is continuous from the midline to the rhinal sulcus. The most medial fibers, those in the supracallosal stria, arborize locally in cingulate cortex and do not branch into dorsal or lateral cortex. The dorsolateral cortex is innervated by an intragriseal NA pathway, which forms a sheet of longitudinal, caudally directed fibers spread across the deep cortical layers. Many of these fibers (Fig. 3) appear to enter the cortex ventrally, rostral to the caudate nucleus (*7*), where they turn dorsally and then caudally within the frontal pole, passing through the frontal cortex. These same fibers continue caudally throughout the longitudinal extent of the hemisphere supplying the cortical NA innervation throughout their trajectory.

The data suggest the existence of a coarse topographic order within the NA innervation of cortex. The topographic order is such that the mediolateral position of a longitudinally directed fiber determines its zone of innervation. Although the lesions were somewhat large, we propose, as a first approximation, that NA fibers innervate a slab of cortex from the frontal to the occipital pole. This topographic relationship has been demonstrated only within the cortex, but it raises the possibility that cell bodies of the locus coeruleus have a topographically ordered projection that may previously have escaped detection by retrograde transport methods because of the unusual trajectory of the NA axons.

Because of this arrangement of fibers, a small lesion can denervate a large area of cortex distant from the lesion. In the extreme case, a frontal lobotomy, as shown here, can denervate the entire dorsolateral cortex, sparing only the medial and perirhinal cortex. Similarly, minor damage to the rostral anterior cingulate cortex would deprive the entire medial cortex of NA innervation. An important implication is that some aspects of the behavioral syndromes that result from medial or dorsolateral frontal ablation may be due to the far-reaching NA deficits that result from such lesions.

The global extent of the tangential, intragriseal noradrenergic axons indicates

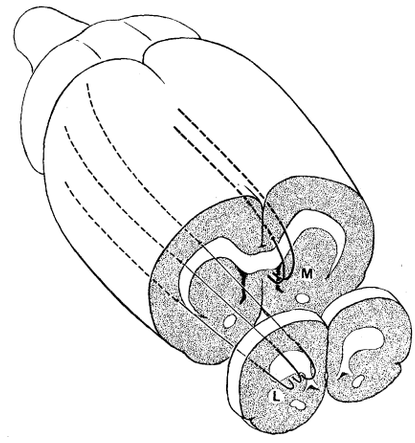

Fig. 3. Trajectory of noradrenergic axons en route to cortex. Abbreviations: *M*, medial NA axons curve over the genu of the corpus callosum and innervate medial cortex; *L*, NA axons pass through the cortex of the frontal pole and turn caudally to innervate lateral cortex.

that the neocortex is organized as a three-dimensional matrix in which systems with tangential and with radial orientations intersect and may interact. The fundamental modular unit of cortical organization is a vertical column of cells with strong radial connections but sparse and short horizontal connections (*8*). The columnar concept does not restrict cortical circuitry to the vertical axis but affords considerable opportunity for nonradial systems to act upon the columns in other ways (*9*). The coeruleocortical system is the first long pathway that has been shown to take advantage of the structural fact that the entire cortex is a horizontally continuous laminated sheet of gray matter. While each column appears to receive specific information via radially oriented afferents (essentially private lines), the tangential noradrenergic fibers intersect a longitudinal array of columns, furnishing this projection with the unique capacity to modulate neuronal activity synchronously throughout a vast expanse of neocortex crossing cytoarchitectural and functional boundaries.

The physiological effect of the NA projection to the cortex depends on the types and distribution of intercellular contacts by which NA axons engage cortical neurons. Because neurotransmitter release may not be restricted to junctional appositions (*10*) and because intracortical NA parent fibers may form synapses *en passage*, the conventional distinction between axons of passage and axons of termination is not simply applicable to this system. Hence, a detailed knowledge of the synaptic organization of NA afferents at the ultrastructural level is needed to determine the extent to which this system may influence cortex by way of specific synapses (*11*) or by diffuse release of transmitter (*12*).

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