24. Standard binding reactions contained 20 mM Hepes-NaOH (pH 7.9), 20 mM tris-HCl (pH 7.9), 50 mM KCl, 2 mM DTT, 7% (v/v) glycerol, bovine serum albumin at 0.5 mg/ml, 2% (w/v) polyvinyl alcohol, and DNA and protein fractions as indicated in the figure legends. Unless otherwise indicated, reactions were incubated for 20 min at 28°C and then separated by electrophoresis at 75 V for 2.5 to 3 hours in a polyacrylamide gel containing 4% acrylamide, 0.1% bisacrylamide, 89 mM tris, 89 mM borate, and 2 mM EDTA.
25. Transcription factor βγ (~20 μg/ml) used in the experiments shown in Figs. 3 and 5 was purified from the livers of 250 rats as described (*5*), except that the acetone fractionation step was omitted, and DEAE chromatography was carried out using a semipreparative (21.5 mm by 150 mm) TSK DEAE-5-PW HPLC column (Beckman).
26. We thank I. R. Lehman and R. Kornberg for critical reading of the manuscript, M. Cannefax for preparing the manuscript, the Drawing Room (Palo Alto, CA) for artwork, E. Travis for technical assistance, and G. Zurawski for a gift of DNA fragments. Supported by grant GM 41628 from the National Institutes General Medical Sciences.

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A Major Direct GABAergic Pathway from Zona Incerta to Neocortex

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Retrograde fluorescent tracers were used to demonstrate a previously unknown but sizable direct γ-aminobutyric acid (GABA)–containing neuronal pathway from the zona incerta to the neocortex in rats. This incertocortical pathway was found to project bilaterally to the entire neocortex and exhibited a rough corticotopic organization. Many of the zona incerta neurons projecting to the parietal and occipital cortices could also be immunohistochemically stained with antibodies to glutamic acid decarboxylase and GABA. Few of these neurons were immunoreactive to tyrosine hydroxylase antibodies, which identify dopamine-containing neurons. Injections in the frontal and entorhinal cortices labeled many neurons near or within the dopaminergic A13 subdivision of the zona incerta. In addition, the incertocortical system was found to be significantly larger during early postnatal (2 to 3 weeks) development. The projection pattern of this newly discovered pathway resembles that of the monoaminergic and cholinergic systems, arising from the brainstem and forebrain, suggesting possible similarities of function.

THE DORSAL THALAMUS OF THE DIencephalon was once considered to be the exclusive source of afferents to the neocortex. However, a number of direct nondiencephalic neocortical afferent systems have been described during the past two decades. These direct ascending systems include the monoaminergic inputs from the locus ceruleus, the raphe nuclei, and ventral tegmental area in the brainstem (*1*), and the cholinergic inputs from the basal forebrain area (*2*). One of the unique features of these transmitter-specific systems is their more diffuse and bilateral projection pattern to all cortical areas as compared to the dorsal thalamic nuclei, which have very specific and ipsilateral connections to different neocortical areas (*3*). These ascending systems are also known to be closely related to early cortical development and plasticity (*4*).

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Although electrical stimulation in the general region of the ventral thalamus produces arousal and cortical desynchronization (*5*), no study has yet demonstrated direct neocortical projections from any region of the ventral thalamus [such as zona incerta (ZI)] (*6*).

We report here the existence of widespread projections from the ZI to the entire neocortex. These projections were discovered through the use of recently developed, very sensitive fluorescent retrograde tracers. Furthermore, in experiments that combined the retrograde tracing with immunohistochemical approaches, many of these incertocortical projecting neurons were found to stain positively for glutamic acid decarboxylase (GAD) or γ-aminobutyric acid (GABA).

Our conclusions are based on a total of 60 rats injected with fluorescent tracers either unilaterally or bilaterally into several cortical areas. The cortical projection pattern of ZI neurons was determined both in adult (n = 40) and young (2 weeks, n = 10; 3 weeks, n = 10) rats. Small injections (0.5 to 1 μl) of either rhodamine-coated microspheres (RCMs) or fluorescein-coated microspheres (FCMs) or Fluoro-Gold were stereotaxically placed into the frontal (4 cases), motor (8 cases), somatosensory (45 cases), auditory (4 cases), entorhinal (4 cases), and visual (15 cases) cortices. After survival times of from 4 to 10 days, the rats were perfused with either 10% formalin or 3.0% paraformaldehyde in 0.1 M phosphate buffer at pH 7.4. Brain sections (30 to 100 μm thick) were cut with a vibratome. Antibodies to the synthetic enzyme GAD and GABA were used as specific markers for GABAergic neurons. Antiserum to tyrosine hydroxylase (TH) was used as a marker for dopamine-containing neurons. Standard immunohistochemical methods, including fluorescence and the modified ABC technique, were used for the identification of neurons containing dopamine and GAD or GABA (*7*). Combined retrograde fluorescent tracers and immunohistochemical methods were also used on the same sections to elucidate the specific transmitter that might be contained in the incertocortical projections (*8*). An epifluorescent microscope (Nikon) was used to visualize the precise location of neurons with fluorescent retrograde tracers.

Whereas the thalamocortical connections revealed in these studies were consistent with those previously reported in the literature, the presence of large numbers of retrogradely labeled neurons in the ZI was unexpected. For example, after dyes were injected into the primary somatosensory cortex (SI), retrogradely labeled neurons were found in the ventroposterior nucleus (VP), the posterior nuclear complex (PO), the centrolateral nucleus (CL), the posterior division of the hypothalamic nuclei (HP), (Fig. 1, A to D), and the ventromedial thalamic nucleus (VM). However, the most intriguing finding was that many cells in the dorsolateral region of ZI were labeled (Fig. 1, B and C). In addition, a few scattered labeled neurons were found in the contralateral ZI and bilaterally in the posterior region of the hypothalamus [as had been previously reported (*9*)]. Injections of tracers into the primary visual cortex (VI) produced fewer retrogradely labeled neurons in ZI than after SI injections, and these were primarily located in the ventrolateral subregions of the ZI, and the hypothalamus (Fig. 1, D to F). Although injections of different colored retrograde tracers placed in the SI and VI cortices yielded two separable clusters of labeled cells in the ZI, a significant overlap between these clusters was observed. Moreover, several double-labeled neurons were identified in this overlap zone. After injections into the entorhinal-temporal cortical areas, labeled neurons were found forming a dense cluster, centered medially around the

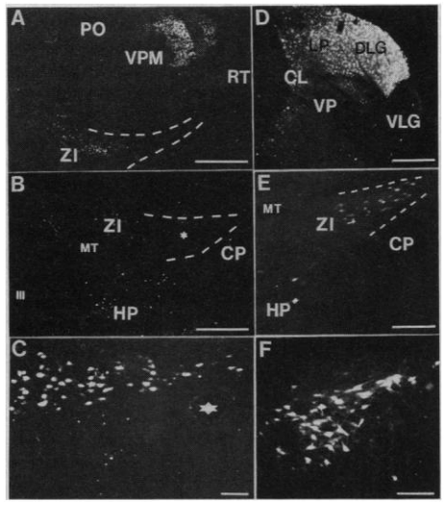

Fig. 1. Fluorescence micrographs of retrogradely labeled neurons in the diencephalon after injections of RCMs into (A to C) the somatosensory cortex and Fluoro-Gold into (D to F) the occipital visual cortex. Note the RCM-labeled neurons located in the dorsolateral subregion of (**A**) the ZI and (**B**) the posterior division of the hypothalamic nucleus. (**C**) A high-power fluorescence micrograph shows numerous labeled cortical projecting neurons in the ZI. The star in (C) marks the same blood vessel as shown in (B). (**D**) Numerous retrogradely labeled neurons were found in the dorsal thalamic nuclei, such as the lateral posterior (LP) and the dorsolateral geniculate nucleus (DLG) after injections of Fluoro-Gold into the visual cortex. (**E**) Dense labeling was found in the extreme lateral subdivision of ZI. (**F**) High-power micrograph shows the clustering of retrogradely labeled cells in the ZI. PO, posterior nucleus; VPM, ventroposterior media nucleus; RT, reticular nucleus of the thalamus; ZI, zona incerta; CP, cerebral peduncle; HP, posterior division of the hypothalamic nucleus; MT, mamillothalamic tract; CL, centrolateral nucleus; VLG, ventrolateral geniculate nucleus; and VP, ventroposterior nucleus. Scale bar, 1 mm for (A), (B), (D) and (E); 50 μm for (C) and (F).

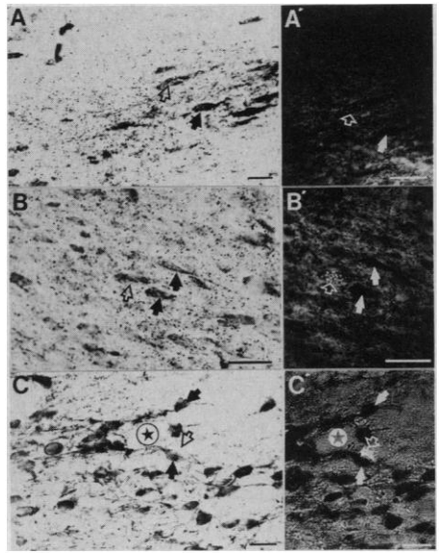

Fig. 3. Bright-field and fluorescence micrographs of ZI neurons retrogradely labeled with RCMs after cortical injections and immunohistochemical staining for (A and B) GAD or (C) TH. Bright-field micrographs (**A**) and (**B**) show immunohistochemically labeled neurons for GAD antibodies in the lateral region of ZI. The open arrows points to retrogradely labeled neurons with RCMs that are also stained with antibodies for GAD. Solid arrows point to neurons only stained for GAD (**A'** and **B'**). RCMs (as indicated by open arrows) are visible in the cytoplasm of GAD-positive neurons. (**C** and **C'**) The same section of the dopamine A13 group in the medial ZI. The open arrow points to an RCM retrogradely labeled neuron located adjacent to several TH-positive neurons (solid arrows). The star marks the same blood vessel in panels (C and C'). Scale bar, 30 μm.

A13 dopamine cell group area of ZI, located ventral to the mamillothalamic tract. Injections centered in the dorsomedial frontal cortex (receiving inputs from the medial dorsal thalamic nucleus) produced a cluster of retrogradely labeled neurons in the A13 area. Moreover, injections placed in the motor cortex produced a distribution of labeled cells resembling that after SI injections. Therefore, a rough corticotopic organization of the incertocortical projections was observed (Fig. 2A).

None of the injected material reached either the underlying white matter or the adjacent structures such as the basal ganglia and the hippocampus. This was verified by the lack of thalamic labeling that would be expected if the tracers had spread to these regions (*10*). Moreover, the same overall pattern of the incertocortical projections was consistently found, irrespective of the types of dyes being used.

As large as this projection is, it is remarkable that the incertocortical ascending system has not been previously reported. One possible explanation lies in the recent finding that the RCM, FCM, and Fluoro-Gold tracers are more sensitive than other retrograde tracers, such as horseradish peroxidase (HRP) (*11*). This difference in sensitivity was verified here in experiments with wheat germ agglutinin (WGA)–HRP as a tracer. Retrogradely labeled neurons in the ZI were identified only in cases where massive WGA-HRP cortical injections were made (*12*). It also appears that this incertocortical pathway does not result from a transneuronal transport of fluorescent dyes. First, the fluorescent tracers that we used are not known to be transneuronal (*13*). The results were independent of the survival time. Finally, no other conceivable transneuronal

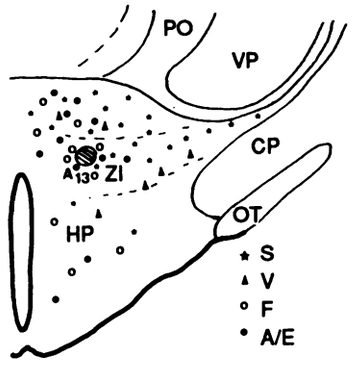

Fig. 2. A summary figure illustrates the corticotopic organization of the ZI projection to the cerebral cortex. The symbols represent the relative density of neurons retrogradely labeled by different cortical injections sites. S, somatosensory; V, visual; F, frontal; A/E, auditory and entorhinal cortices; and OT, optic tract. The hatched area identifies the mamillothalamic tract. The dopaminergic A13 area is located ventral to the mamillothalamic tract.

labeling (for instance, in retina or trigeminal nuclei) was observed.

To determine which neurotransmitter may be contained in this incertocortical system, we combined immunohistochemical staining for GAD, GABA, and TH antibodies with retrograde labeling. Numerous GABAergic neurons were identified in the lateral segment of the ZI (Fig. 3), and many of these were observed to be also labeled with beads of retrogradely transported RCMs (Fig. 3, A and B, open arrows). In contrast, few double-labeled neurons were found in the dopaminergic A13 subregion of ZI, when injections were made in SI and VI cortices. After these injections, neurons in the A13 region were typically found to contain either RCMs or TH, but not both, even though these subgroups of cells overlapped each other (Fig. 3C). Nevertheless, injections centered in the dorsomedial frontal and in the entorhinal cortices did produce a cluster of retrogradely labeled neurons centered in the A13 area. This finding strengthens the possibility that dopaminergic neurons in the A13 region of the ZI may project to restricted areas of the cortex. In fact, there have been reports that GABAergic neurons in the ZI may also contain dopamine (*14*). Furthermore, since not all retrogradely labeled neurons were GAD or GABA immunoreactive, we cannot exclude the presence of other neurotransmitters or modulators in those projecting neurons. For instance, somatostatin has been reported to be colocalized with GABA in neurons of other regions of the central nervous system. Thus, they may also be colocalized in the lateral subregion of the ZI as well (*15*).

What is the physiological significance of this GABAergic incertal pathway to cortex? Recent preliminary evidence indicates an increase of spontaneous activity and enlarged receptive fields of the barrel cortical

neurons after chemical lesions of this region of the ventral thalamus (*16*). Our results directly support the idea that ZI may provide inhibitory influences upon cortical neurons.

The ZI is located in the ventral thalamus and matures earlier than the dorsal thalamus (*17*). Since cholinergic, monoaminergic, and GABAergic systems are known to influence cortical development and plasticity (*4*), we investigated possible developmental effects on the connection between the ZI and the sensory neocortex. Fluorescent dyes were injected into the SI and VI cortices of 2- and 3-week-old rats. The retrograde labeling pattern in the ZI of these animals was compared with equivalent experiments in normal adults. The general region of the ZI was defined in young and adult animals with cytochrome oxidase (Fig. 4A). The number of cells labeled in 100-μm-thick sections through the ZI, following comparable small injections of RCMs in the barrel fields of SI (Fig. 4, B and C), was significantly higher for 2-week-old (331 ± 49) and 3-week-old (242.7 ± 23) rats relative to adults (112.66± 18.4) (*18*). This greater labeling of ZI in young animals (Fig. 4, B and C) was found in every case studied. Thus, a dense projection from the ZI to the neocortex is present during a critical period for maturation of cortical circuits.

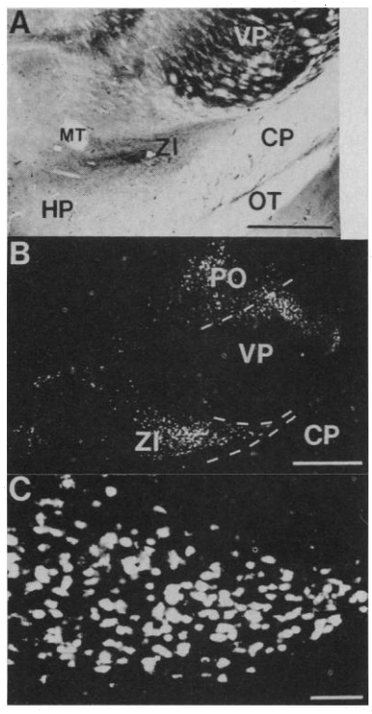

Fig. 4. (**A**) Low-power photomicrograph of the ZI stained with cytochrome oxidase in an adult animal. Note the diversity of staining within the ZI and in particular the intense staining of the VP. Abbreviations as in Figs. 1 and 2; MT, mamillothalamic tract. (**B**) Low-power fluorescent micrograph showing retrogradely labeled neurons in the diencephalon of a 2-week-old rat after RCM injections placed in the barrel fields of SI. Note the extensive labeling in the dorsolateral region of the ZI. (**C**) High-power micrograph of the extensive labeling in the dorsolateral subregion of ZI from the same animal as in (B). Scale bar, 1 mm for (A) and (B); 50 μm for (C).

In summary, ZI, the "unknown zone," appears to give rise to a major cortical projecting system. Since the ZI is known to receive major inputs from the cortex, the dorsal column nuclei, the trigeminal nuclear complex, and the intermediate and deep layers of the superior colliculus (*19*), it may provide an important link between ascending sensory and motor systems and the cerebral cortex. In addition to the neocortex, the ZI also projects to a variety of brainstem structures and the basal ganglia (*20*). In particular, GABAergic neurons in the ventrolateral subregion of ZI project directly to the superior colliculus (*21*). Conceivably, single ZI neurons may collateralize to provide GABAergic inputs to both neocortex and brainstem structures. Such widely divergent projection pattern is consistent with the notion that the ZI of the ventral thalamus may function in a generally similar fashion to the monoaminergic systems of the brainstem and the cholinergic system of the basal forebrain.

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counted without knowledge of the age group. For each case, the number of cells labeled in ZI was obtained by summing the results of the three rostral to caudal levels. For each age, results were expressed as means and standard deviations. Means were compared with the use of one-way analysis of variance. This analysis showed that the young animals (2 and 3 weeks old) contained significantly more retrogradely labeled cells in the ZI than normal adults ($P < 0.01$).

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Attentional Modulation of Neural Processing of Shape, Color, and Velocity in Humans

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Positron emission tomography (PET) was used to measure changes in regional cerebral blood flow of normal subjects, while they were discriminating different attributes (shape, color, and velocity) of the same set of visual stimuli. Psychophysical evidence indicated that the sensitivity for discriminating subtle stimulus changes was higher when subjects focused attention on one attribute than when they divided attention among several attributes. Correspondingly, attention enhanced the activity of different regions of extrastriate visual cortex that appear to be specialized for processing information related to the selected attribute.

PEOPLE CAN RESPOND TO ONLY A small amount of the sensory information present at any moment. Selection of information is necessary to ease the computational problems introduced by the enormous number of signals present at the sensory surfaces and to ensure that people respond to stimuli that are relevant to their goals.

Although many studies have investigated visual attention to spatial location (*1*), attention can be focused along several other dimensions (or attributes). People can attend to, or "look for," a specific kind of visual information (for example, a red hat worn by a friend in a crowd). Attending to an attribute improves accuracy on visual detection or discrimination tasks, particularly under conditions of near-threshold discriminability (*2*).

Attending to a visual attribute, such as its color, might be expected to modulate neuronal activity in brain areas that are specialized for processing that attribute. Such feature-specific changes have been reported for color and orientation in monkey V4 (*3*), an area in the occipitotemporal system that is critical for object recognition (*4*). Both behavioral and electrophysiological analyses also indicate that these modulations are stronger during difficult discriminations (*5*).

Selective changes in neural activity may occur in areas of the visual cortex other than V4 and apply to attributes other than color and orientation (for example, velocity) (*6*). Cueing subjects to different dimensions (color, shape, or velocity) might therefore modulate different regions of extrastriate visual cortex, each specialized for processing a particular dimension. We tested this hypothesis in normal subjects with PET by measuring changes in local blood flow (BF), which correlate with changes in neuronal activity (*7*). PET enabled us to monitor activity simultaneously from several brain regions, and therefore determine the effect of attending to different stimulus dimensions on multiple extrastriate visual regions.

We developed a psychophysical task to study the influence of visual attention on the discrimination of subtle stimulus changes in the shape, color, or velocity of a visual stimulus. We then measured BF changes while subjects were performing the task. A same-different paradigm was used. On each trial, subjects fixated a small spot and were presented with two 400-ms stimulus frames, separated by a 200-ms blank display interval (Fig. 1). The stimulus frame was a spatially random distribution of small bars identical in color and shape, moving horizontally as a coherent sheet either to the left or to the right. The direction of motion was constant within a trial but was randomly shifted across trials. The shape, color, and velocity of all elements might independently change between the first and the second frame. The subject's task was to compare the first stimulus frame with the second, and report (by a key-press) if the two frames were same or different for a particular dimension, specified at the beginning of each experimental block. Stimulus changes were close to threshold as assessed for each subject in a separate psychophysical session (*8*).

In three blocks of trials subjects discriminated a stimulus change of either shape, color, or velocity (selective attention) (*9*). Half the trials were "different" and contained a change in the specified dimension, and half the trials were the "same." Same and different trials also contained (in equal proportions) stimulus changes in zero, one, or two of the unspecified or irrelevant dimensions. For instance, during same or different trials in a color block, velocity and shape might stay constant in both frames, velocity might change, shape might change, or both velocity and shape might change. In a fourth block, subjects detected changes in any attribute, dividing attention across dimensions (divided attention). In this case none of the stimulus dimensions varied in half of the trials (same trials) and changes in only one dimension (that is in color, shape,

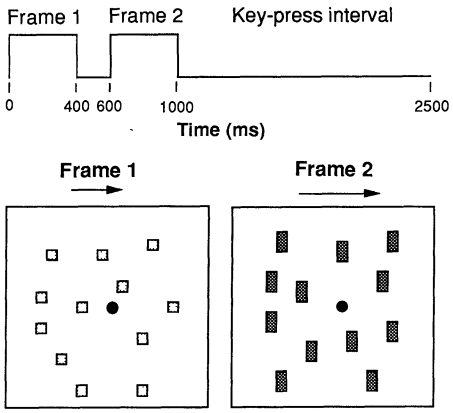

Fig. 1. The size of each element was either 0.8° × 0.8° of visual angle or the just noticeable difference obtained by modifying the length and width. Colors were either red or green, or the respective just noticeable difference in hue obtained by, respectively, adding a small amount of green or red. Velocity was either 18 degrees per second or the just noticeable difference obtained by increasing the velocity. Background luminance was 0.18 foot lamberts (ft-L). The luminance for a single element was about 3.4 ft-L in the red range, and 10.2 ft-L in the green range.

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