Siamese Cat: Altered Connections of Visual Cortex

Abstract. *In Siamese cats, each side of the brain receives a retinal input serving part of the ipsilateral visual field as well as the normal contralateral field representation. Both corticothalamic and cortico-cortical projections are systematically rearranged, but while one is retinotopically appropriate, the other fails to make a distinction between ipsilateral and contralateral fields. Different rules appear to govern the development of these two sets of connections.*

One of the most characteristic attributes of the brain is the precision of its internal connections. In the visual system, for example, the many maps of external visual space that exist within the brain are interconnected by sets of fibers joining visuotopically corresponding points. What mechanisms bring these connections about (*1*)? One possibility is that central connections form on the basis of topographical information that reaches the brain from the retina. Alternatively, they may form in accordance with some internal program independent of the periphery. The visual system of the Siamese cat offers an opportunity to study this problem, since the brain of this animal is presented with an abnormal input from the retina (*2*). Rearrangements in the afferent visual pathways of Siamese cats have already been described (*3–7*). These findings tend to support the hypothesis that information from the retina is used in the formation of central connections. We report here an anomalous connection with the visual cortex of Siamese cats, which may cast further light on developmental mechanisms in the cerebral cortex.

In common cats, the primary visual cortex (area 17) on each side of the brain carries a binocular map of the contralateral half of the visual field. The manner in which this is generated is shown in Fig. 1. The first step in this sequence involves the setting up of two separate monocular maps in different laminae of the lateral geniculate nucleus (LGN), the visual relay nucleus of the thalamus. Fibers from the nasal half of each retina cross in the optic chiasm and innervate cells in the dorsalmost geniculate lamina, called lamina A. Fibers from the temporal half of each retina remain on the same side and innervate geniculate lamina A1. The two maps are in register, and cells at corresponding points in the two laminae project to the same region of the visual cortex. The most medial cells in the LGN represent the vertical midline of the visual field, and project to the border of area 17 where it abuts the secondary visual cortex, area 18. Cells in more lateral parts of the LGN, representing more peripheral parts of the visual field, project to regions further within area 17.

In Siamese cats, a mutation at the albino locus (which also produces the characteristic coat color) is responsible, through some unknown mechanism, for a misrouting of many optic nerve fibers. Fibers from a region of retina stretching from the vertical midline to a point 15° to 20° into the temporal retina cross in the chiasm and terminate in the medial portion of lamina A1 on the wrong side of the brain (*3, 8*). This gives the LGN a representation of part of the ipsilateral visual field in addition to its normal contralateral field representation in lamina A. The misrouting is orderly: Corresponding points, one above the other, in laminae A and A1 represent mirror-symmetric positions in the contralateral and ipsilateral visual fields but in the contralateral eye only.

Physiological mapping studies of the visual cortex suggest that this abnormal representation of the visual field in the LGN is handled in one of two alternative ways. We are concerned here with only one of these, the "Boston" projection pattern (*9*) [so-called because it was first described at Harvard Medical School (*6*)]. This pattern involves a reorganization of the normal geniculo-cortical projection in such a way as to preserve visual field continuity: The abnormal representation of the ipsilateral field is inserted at the border between areas 17 and 18, and the vertical meridian representation is displaced further into area 17 proper.

We have verified this reorganization anatomically, using the retrograde axonal transport of horseradish peroxidase (HRP) injected into the visual cortex from a recording micropipette (*10*). In three Siamese cats, the enzyme was injected at the 17–18 border (*11*), and receptive fields recorded there ranged from 10° to 15° into the ipsilateral visual field, indicating the Boston pattern. Labeled cells were subsequently found in the medial portion of LGN lamina A1 [which receives the abnormal representation of the ipsilateral visual field (Fig. 1)]. No labeled cells were found in lamina A. In three additional Siamese cats, injections of HRP were made in area 17 at visual field positions of 12° to 20° into the contralateral field. In these animals, labeled cells were found in LGN lamina A but not in the medial, abnormal portion of A1. These results confirm the geniculocortical projection pattern inferred from the physiological recordings (Fig. 1) and

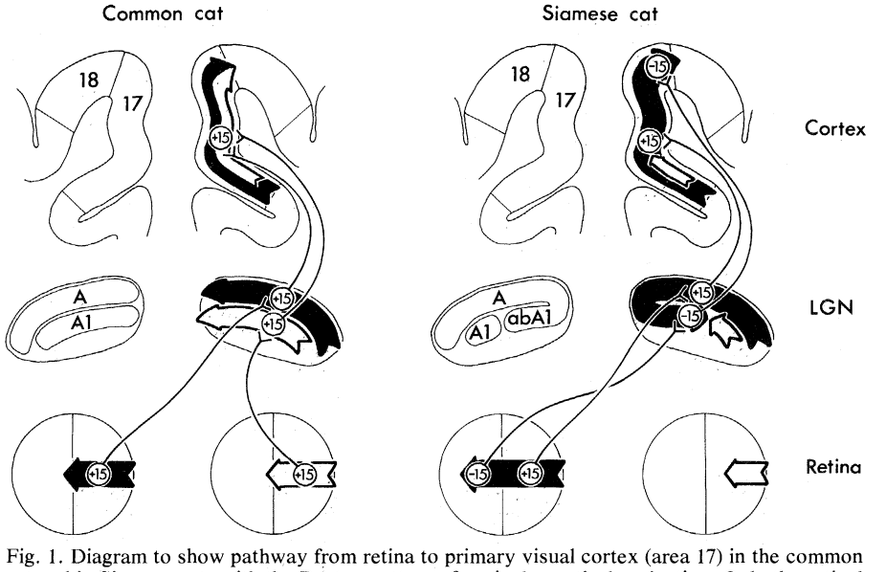

Fig. 1. Diagram to show pathway from retina to primary visual cortex (area 17) in the common cat and in Siamese cats with the Boston pattern of geniculo-cortical projection. Only the retinal projections to the right hemisphere are shown, with the contribution from the left retina indicated by a solid arrow and that from the right retina as an open arrow. The line dividing each retina is the representation of the vertical midline of the visual field. The figures +15 and −15 indicate the position of neurons whose receptive fields, with reference to the right side of the brain, are situated 15° contralateral (+15) or 15° ipsilateral (−15) to the vertical midline. In the Siamese cat the LGN lamina *A1* is broken into two regions: a medial region (*abA1*) receiving the abnormal representation of the ipsilateral field, and a lateral region (*A1*), which receives what remains of the normal contralateral field representation from the ipsilateral eye (open arrow). Other subsidiary retinal projections to the LGN (to the C laminae and medial interlaminar nucleus) have been omitted for simplicity.

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contrast with the pattern seen in common cats, in which an HRP injection anywhere in the visual cortex labels cells at corresponding points in laminae A and A1.

As a consequence of this rearrangement, the 17-18 border region in the Siamese cat carries a visual field representation that is different from normal. The question arises whether the further connections made by cells in this region are also altered or retain the pattern seen in the common cat. To study this question, we traced their efferent projections autoradiographically using the anterograde axonal transport of [^{3}H]proline injected from a recording micropipette (*12*). In three common cats, injections at the 17-18 border (identified histologically and also by the presence of receptive fields at the vertical midline) gave rise to a recurrent projection to the LGN, which terminated, as expected, in both laminae A and A1 at the medial edge of the nucleus. Within the cortex, local connections from the 17-18 border extended diffusely a few millimeters into area 17 and 18, but the nearest major projections were to the lateral part of area 19 on the same side of the brain and, via the corpus callosum, to the opposite 17-18 border. These connections link retinotopically corresponding regions.

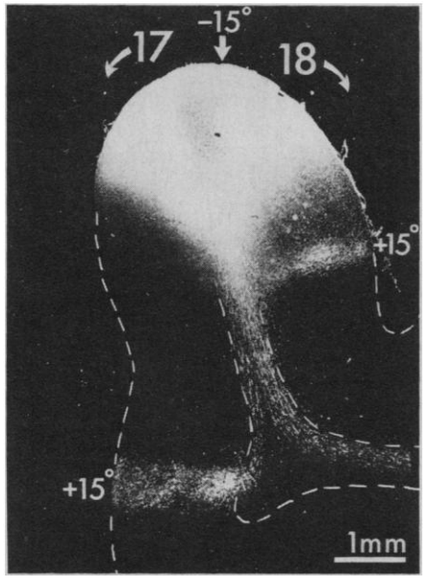

Fig. 2. Autoradiograph of visual cortex of a Siamese cat which received an injection of [^{3}H]proline at the 17-18 border. In this dark-field micrograph, regions containing silver grains appear white, except for the center of the injection site which is so heavily labeled as to nullify the dark-field effect. The position of the 17-18 border (vertical arrow) was determined histologically in an adjacent section stained with cresyl violet. A projection site within area 17 is visible (bottom left). From physiological mapping studies this site is known to represent a visual field position approximately 15° into the contralateral field (+15), that is, mirror-symmetrical to the field position represented at the injection site (−15). Area 18 carries a second, more compressed representation of the visual field, and an anomalous projection is evident there too (middle right, +15). Medial is to the left, and dorsal is up.

Similar injections made at the 17-18 border (Fig. 2) in five Siamese cats gave rise to a quite different projection pattern. Receptive fields recorded at the injection sites were not at the vertical meridian but were 10° to 15° into the ipsilateral visual field, indicating the presence of the Boston pattern. The recurrent projection to the LGN is shown in Fig. 3. It was restricted to the medial portion of lamina A1, which carries the abnormal representation of the ipsilateral field. Lamina A, which carries the normal representation of the contralateral field, was almost unlabeled. Thus there appears to be a rearrangement of the corticogeniculate pathway so that, as in common cats, retinotopically corresponding points are connected.

Within the visual cortex, on the other hand, an unexpected projection pattern was seen in four of the five cats. The 17-18 border region projected massively to zones deep within areas 17 and 18 (Fig. 2). The zones represent a region in the contralateral field approximately 15° from the vertical midline (*6*). These cortico-cortical projections, therefore, appear to link regions representing different, though mirror-symmetric, visual field positions (*13*).

In two of the cats, in which the injections had heavily labeled the entire thickness of the cortex, label at the projection sites formed a column extending through all six cortical layers, but with distinctly lower grain density in layer IV (see Fig. 2). This laminar pattern is characteristic of cortico-cortical projections in common cats. In the third cat, the injection affected primarily cortical layers I to III and label at the projection site was also in the upper layers. In the fourth cat, the injection was centered in layer VI and the label in the projection zone was found primarily in layers V and VI. Some laminar organization therefore appears to exist within the overall projection. In the fifth Siamese cat, this projection was not seen at all.

Because of the known variability among Siamese cats, we wished to demonstrate the geniculo-cortical and cortico-cortical projection patterns in the same animal. In one of the animals that received an injection of [^{3}H]proline at the 17-18 border (receptive fields were 14° ipsilateral in this case), we also made an injection of HRP within area 17 at visual field position 12° contralateral. As expected, the HRP injection site was labeled autoradiographically, indicating that it received an input serving the ipsilateral visual field from the 17-18 border; and peroxidase-labeled neurons in the LGN were found only in lamina A, indicating that the same cortical region received a representation of only the contralateral field from the LGN (*14*).

The callosal projection to the opposite hemisphere also differed from that seen in common cats. As previously reported (*7*), most of the fibers terminated far within areas 17 and 18, probably linking retinotopically corresponding regions in the two hemispheres. However, a smaller number of fibers terminated in a discrete patch at the 17-18 border—that is, at the representation of the mirror-symmetrical locus in the visual field.

The altered corticogeniculate and cortico-cortical projections in Siamese cats further illustrate the cascade-like rewiring of the central visual pathways that follows the initial error at the optic chiasm. The rearrangement of the corticogeniculate pathway is consistent with the well-known principle that connections are formed between brain regions representing the same point in the periphery, and it indicates the importance of information derived from the retina in their development. The anomalous cortico-cortical connection, on the other hand, defies this principle and links noncorresponding though mirror-sym-

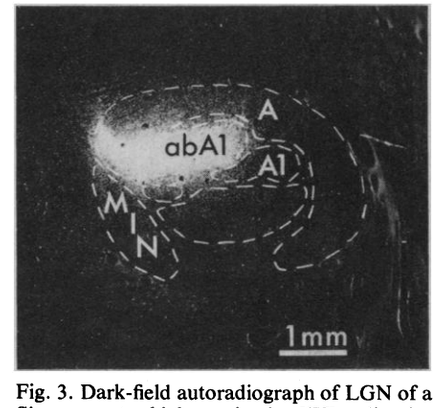

Fig. 3. Dark-field autoradiograph of LGN of a Siamese cat which received a [^{3}H]proline injection at the 17-18 border. A projection is evident to the abnormal segment of lamina A1. Only scattered grains are seen in lamina A, in this and other sections, indicating that the corticogeniculate projection is to the retinotopically appropriate locus and not to the mirror-symmetric visual field locus in lamina A. The laminar boundaries were identified in the same section after photography, by counterstaining with cresyl violet. Abbreviation: *MIN*, medial interlaminar nucleus. Medial is to the left and dorsal is up.

metric visual field loci. It is especially remarkable that a single region of cortex distinguishes between ipsilateral and contralateral visual fields in its recurrent connections with the LGN, but fails to do so in its associational connections (*15*). The two projections may, however, arise from different populations of cells, as is known to be the case in common cats (*10*).

The difference in the behavior of the two projections suggests that the rules governing the formation of these two sets of connections are different. We suggest that in the formation of associational connections, positional information from the retina is still used, but the sign of the receptive field position—left or right of the vertical midline—is ignored, and only distance from the midline is considered. This relaxation of specificity would not lead to any wrong connections in common cats, since in these animals each hemisphere receives input only from the contralateral half-field. This interpretation must be viewed with some caution, however, since it is based on the assumption that only optic nerve decussation is directly affected by the genetic mutation and that more central visual structures develop according to normal rules. It could be put on a more secure footing if the same misrouting could be produced in common cats, perhaps by fetal surgery.

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9. In the alternative "Midwestern" pattern, the geniculo-cortical projection is not rearranged, but the ipsilateral visual field input to the cortex appears to be functionally supressed (*4*). It has recently been suggested that the Boston and Midwestern patterns can coexist in different regions of the same animal's cortex [M. L. Cooper, G. G. Blasdel, J. D. Pettigrew, *Assoc. Res. Vision Ophthalmol. Abstr.* (1978), 216]. Our study was confined to the cortical representations of the horizontal meridian and inferior visual fields, and in these regions only the Boston pattern was observed.
10. C. D. Gilbert and J. P. Kelly, *J. Comp. Neurol.* **163**, 81 (1975).
11. The 17-18 border was determined during the recording session by locating the maximum excursion into the ipsilateral visual field and was later identified histologically.
12. S. LeVay and C. D. Gilbert, *Brain Res.* **113**, 1 (1976).
13. We were unable to determine whether the projections from the 17-18 border to area 19 and the Clare-Bishop area were also rearranged because the visuotopic maps of these areas in Siamese cats have not been studied.
14. The demonstration of these anomalous projections from the 17-18 border into area 17 may provide an explanation for a puzzling observation that has occasionally been made in Siamese cats showing the Boston pattern of reorganization. While mapping the contralateral field representation within area 17, Hubel and Wiesel (*6*) noted in some animals a few groups of cells whose receptive fields were located not in the contralateral field but at the mirror-symmetrical locus in the ipsilateral field. Some cells even had "mirror fields," that is, they had one receptive field in each half of the visual field. It was suggested that these cells received a direct geniculate input from neurons in LGN lamina A1 whose axons, for some reason, had not been redirected to the region of the 17-18 border. The present results suggest another interpretation, namely, that the "Boston" rearrangement of the geniculo-cortical projection is complete and that the ipsilateral field input to the mirror-field cells is supplied by the anomalous cortico-cortical projection described above. We should emphasize, however, that mirror fields are uncommon and were not observed in the animals studied here. Furthermore, it is conceivable that a few cells in the medical, abnormal portion of lamina A1 did project to the cortical representation of the contralateral visual field, but the HRP method was insufficiently sensitive to detect them.
15. In the formation of the callosal connections, the tendency is to make a correct choice between ipsilateral and contralateral visual field locations, but some confusion evidently arises.
16. We thank D. Hubel, T. Wiesel, M. Stryker, and P. Patterson for their criticisms of the manuscript. Supported by NIH grants EY R01-1960 (to S.L.), EY 05172 (to C.J.S.), and EY 00606 (to T. N. Wiesel).
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β-Adrenergic Regulation of Adenosine 3′,5′-Monophosphate Concentration in Brain Microvessels

Abstract. *Norepinephrine increases the concentration of adenosine 3′,5′-monophosphate (cyclic AMP) in an incubated suspension of brain microvessels. This response can be matched by other drugs that stimulate the β receptors, but the α-adrenergic agonist phenylephrine is without effect; β-adrenergic blockade abolishes the response while α-adrenergic blockade produces no change. The data support the contention that cerebral capillary function is subject to adrenergic neural control.*

Precise control of brain volume, through adjustment of cell water and electrolyte content, is important for the normal function of the brain not only because it is confined in the rigid and indistensible environment of the skull (*1*) but also because changes in cell volume may affect important functional relationships between cells (*2*). This volume homeostasis must be achieved in the face of the fluctuating osmotic and hydrostatic forces imposed by the incoming blood supply while respecting functionally critical ionic gradients within the brain.

The capillary endothelium, the primary barrier between blood and brains has several features common to membranes known to regulate water and electrolyte permeabilities, such as trout gill, toad urinary bladder, frog skin, rabbit gallbladder, and mammalian distal nephron (*3*), and may have an important role in regulation of brain volume and environment. There is some indication that brain vascular function is under neural influence; especially notable is the change in water permeability of the brain vasculature in response to adrenergic stimulation or centrally administered vasopressin (*3*). New techniques available for the preparation of very pure microvascular tissue from brain tissue now allow direct study of the pharmacology of microvessels in vitro to determine how capillary function might be modulated. In the experiments reported here we measured the effects of neurotransmitters and vasopressin on adenosine 3′,5′-monophosphate (cyclic AMP) concentrations in isolated microvessels of brain. The cyclic AMP system has been closely linked to some neurotransmitter receptors, and there is ample evidence relating this substance to hormone-induced changes in water and electrolyte permeability in other tissues (*4*).

Brain microvessels were prepared from male Sprague-Dawley rats (120 to 250 g) by the method of Goldstein *et al.* (*5*). We examined each preparation of microvessels by phase-contrast and dark-field microscopy to determine the nature and proportion of cell types present. We observed virtually no contamination by neuronal elements. The difference between smooth muscle and endothelial cells was clear in dark field, and we used only those preparations in which muscular vessels were estimated to constitute less than 5 percent of the isolated tissue.

In each experiment, tissue isolated from cerebral cortices of four to six rats was pooled and suspended in Krebs-Ringer bicarbonate buffer previously equilibrated with 95 percent O_2 and 5 percent CO_2. Portions (250 μl) of this tissue suspension containing approximately 30 μg of protein were incubated at

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