Serendipity and the Siamese Cat: The Discovery That Genes for Coat and Eye Pigment Affect the Brain

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Abstract

One day in the late 1960s, Ray Guillery was examining brain sections through the visual thalamus of cats, and he recognized that the arrangement of layers in the lateral geniculate nucleus (LGN) of one cat was strangely abnormal. The cat was identified as a Siamese cat, one of a breed selected for its unusual coat color, with reduced pigment over much of the body and eyes. This chance observation and the recognition of its significance led to a broad-ranging series of investigations. These experiments showed that the lack of normal levels of pigment in the retina in Siamese cats (and other hypopigmented mammals) was the critical factor in the misdirection of many of the projections of the retina to the brain, the nature of the projection error, and the developmental consequences of the relay of the misdirected retinal inputs to visual cortex. As a result, we have a better understanding of how the brain forms proper connections and of the neural basis of visual problems in albino humans.

Key Words: albino; lateral geniculate nucleus; nystagmus; retina; superior colliculus; vision; visual cortex

Introduction

A gene mutation in Siamese cats produces their desirable coat pattern by being temperature sensitive. The cooler skin of body extremities produces normal amounts of pigment (melanin) resulting in the dark ears, paws, tail tip, and snout, while the rest of the skin and retina produce little pigment, resulting in the pale coat and blue eyes typical of the breed. Siamese cats play and hunt much like other cats, and usually nothing seems wrong with them. Most observers would never suspect from their behavior that the mutated gene that produces their attractive coat and eye color is also responsible for a grossly abnormal visual system. One hint that coat and eye color and vision may be linked is that some Siamese cats have noticeably misaligned eyes. Given that cross-eyed cats have little value to breeders, one would think that this undesirable trait would have been eliminated, while keeping the pale coat and blue eyes. Despite the efforts of breeders, many Siamese cats continue to be cross-eyed. The first indication of why this occurs was the result of a chance observation by the neuroanatomist Ray Guillery, whose laboratory was located down the hall from mine at the University of Wisconsin. His initial insights led to an explosive research effort that has given us a better understanding of how the visual system develops, how axons are guided to their proper targets, and how mistakes in brain connections may be partially corrected in development.

In the late 1960s, Ray Guillery was very interested in determining how the lateral geniculate nucleus (LGN[1]) of the visual thalamus of cats is organized. The LGN of each cerebral hemisphere is a nucleus that receives axons from neurons in both eyes and has neurons that send axons to visual cortex to start the process of visual perception. In order to achieve binocular vision (see Figure 1 for the binocular field of cats), parts of the retina of both eyes that view either the right or left half of the visual field project to either the left or right LGN, respectively (Figure 2). Thus, each LGN receives information via both eyes from the contralateral visual hemifield. However, the inputs from each eye are kept strictly separate at this level, and they are not combined until they are relayed by LGN neurons to visual cortex. To do this, the inputs from each eye are precisely aligned by retinal position in adjoining sheets of neurons (layers) in the LGN so that separate, but adjacent, groups of neurons in the layers for each eye view nearly the same locations in visual space. The adjacent neurons project to the same or adjacent locations in visual cortex, where information from the two eyes is combined, and small disparities in viewing angle of the two eyes allow stereoscopic vision—one of the important sources of depth perception. Different species of mammals have different numbers and arrangements of LGN layers, because types of retinal input as well as inputs from the two eyes are isolated in different layers (Kaas et al. 1972). Normal cats have two main layers—a dorsal A layer, with inputs from the contralateral eye, and a ventral A1 layer, with inputs from the ipsilateral eye. In brain sections through the LGN, these layers are easily recognized by an experienced investigator as two parallel sheets of neurons separated from each other by a narrow band of fibers, much as two slices of bread may be separated by a thin slice of cheese.

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[1]Abbreviations used in this article: LGN, lateral geniculate nucleus; V1, primary visual cortex.

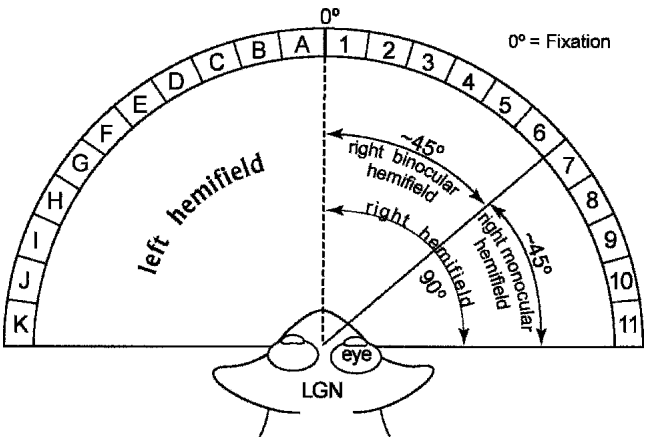

Figure 1 Visual field of cats in numbered or lettered segments reveal (in Figures 2 and 3) how these segments fall on the retina of each eye and are relayed to representations of the visual field in the lateral geniculate nucleus (LGN) of the visual thalamus, and then to primary visual cortex. For the sake of simplicity, only the horizontal plane of vision is considered.

What Ray Guillery noticed one day was that the LGN of one cat was strangely abnormal (Guillery and Kaas 1971). The A layer appeared normal, but the medial position of the A1 layer was fused with the A layer, and the medial portion of the A1 layer was separated from a lateral portion. In addition, the retinal projection pattern indicated that the A layer received inputs from the contralateral eye, as in normal cats, but the fused medial segment of the A1 layer also, and incorrectly, received inputs from the contralateral eye. Only the most lateral segment of layer A1 received input, as it should, from the ipsilateral eye. Because the abnormal LGN was from a Siamese cat, Guillery surmised that all Siamese cats have abnormal retinal projections, and that this characteristic is related in some way to the fact that they are often cross-eyed (see Guillery et al. 1974). The publication of evidence that Siamese cats have abnormal retinal projections (Guillery 1969) intrigued a number of visual neuroscientists and generated numerous research questions, as addressed below.

Question #1: Why is the contralateral retinal projection abnormally large?

In Siamese cats, part of the temporal retina that normally projects to the ipsilateral LGN, projects instead to the contralateral LGN (Figure 3). This characteristic was suggested by the fact that the projection to the contralateral LGN was abnormally large and abnormally included half of the A1 layer (Guillery 1969). As a fortuitous result of being researchers in the same building, Guillery and I soon collaborated to determine that the abnormal projections originate from a vertical strip of retina 20 to 25° wide, just temporal to the nasal half of the retina that normally projects to the contralateral LGN (Guillery and Kaas 1971; see Cooper and Pettigrew 1979 for further details). The vertical line on the retina where ganglion cells switch from projecting to the contralateral LGN to projecting to the ipsilateral LGN is called the line of decussation, and this line was moved approximately 20° into the temporal retina in Siamese cats (Stone et al. 1978). The supposition that this abnormally large retinal projection to the contralateral LGN was somehow related to the greatly reduced pigment of the retina was reinforced by the earlier finding of Ray Lund (Lund 1965; also see Lund et al. 1974) that albino rats have an abnormally small ipsilateral projection from the retina. However,

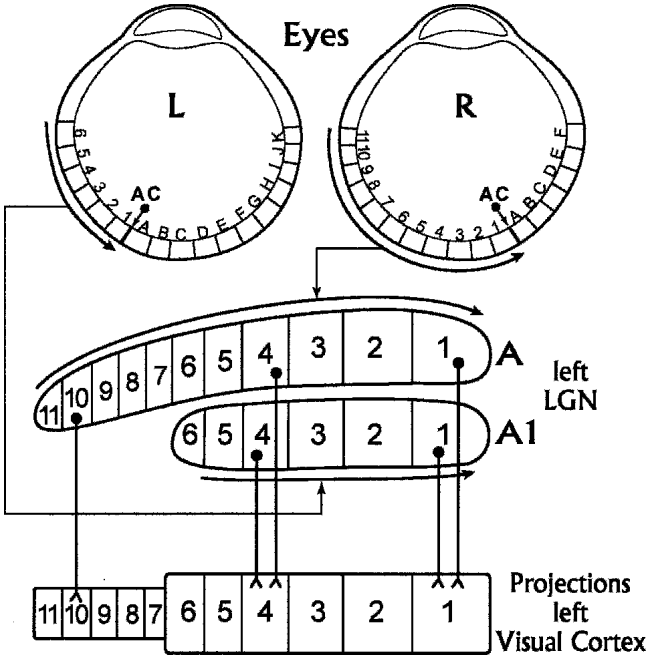

Figure 2 Representation of the visual field in the lateral geniculate nucleus (LGN) and primary visual cortex of normal cats. Normally, the area centralis (AC, equivalent to the human fovea) of the retina of each eye is directed toward the point of fixation (0° in Figure 1). Retina nasal to the AC projects to the LGN of the opposite (contralateral) side of the brain, while retina temporal to the AC projects to the LGN of the same (ipsilateral) side of the brain. Here, only the projections from the left (L) and right (R) eyes to the left LGN are shown. The projection pattern from each eye preserves the order of the visual image on the retina, and the two retinal representations of the contralateral visual hemifield, or the binocular part of it, are precisely aligned in adjoining layers of the LGN (layer A for the contralateral eye, 1-11, and layer A1 for the ipsilateral eye, 1-6). As more projections originate from central than peripheral parts of the retina, the LGN segments for central vision (1-3) are larger than those for peripheral vision (9-11). Neurons in both layers project in aligned patterns to visual cortex, where most neurons respond to inputs from matching locations in the visual fields of both eyes, providing the neural substrate for binocular vision and stereopsis. The monocular segment of visual cortex receives input only from layer A. Dots with lines represent a few of the projecting neurons.

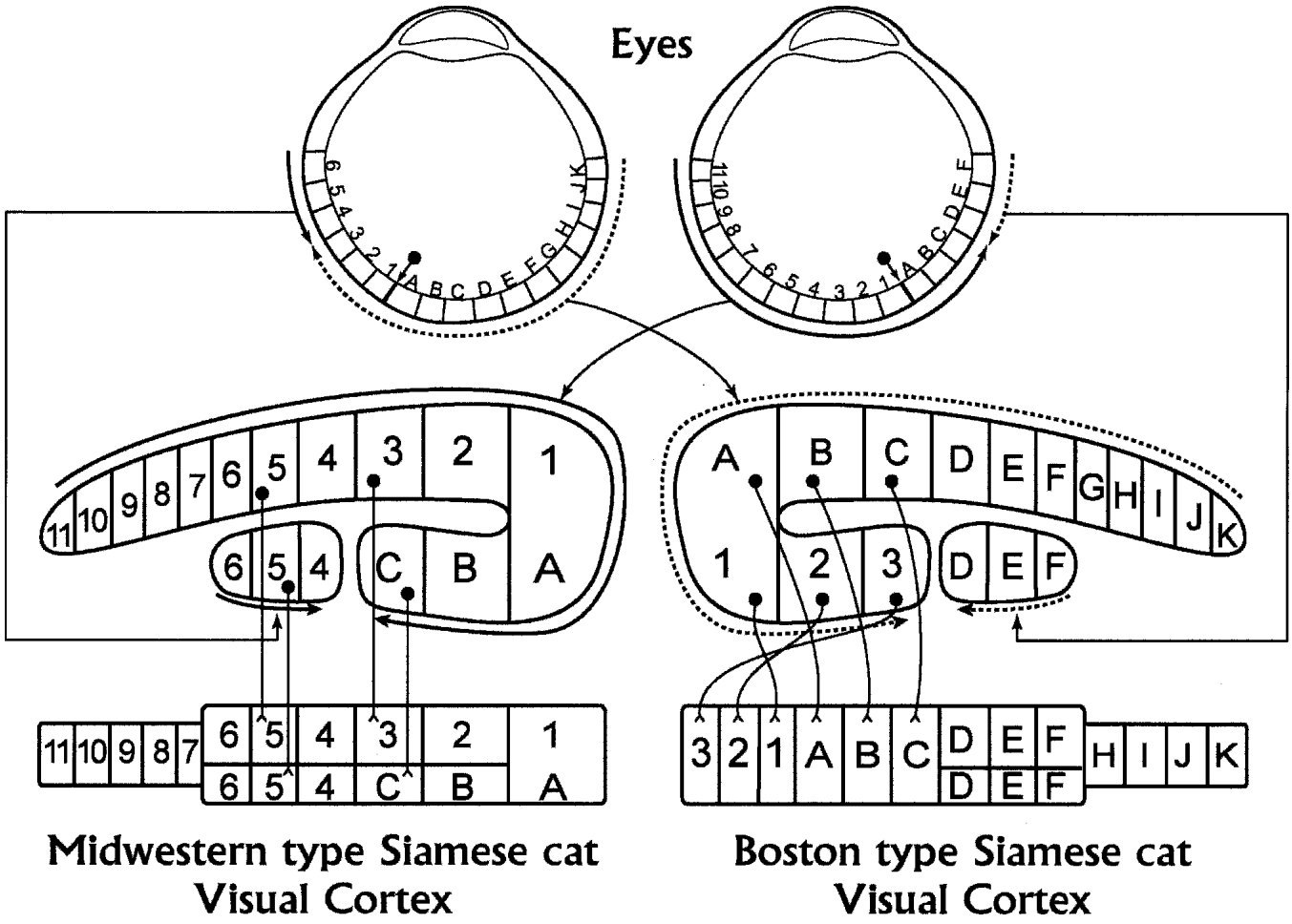

Figure 3 Altered representations of the visual field in the LGN and visual cortex of Siamese cats. A projection error in these cats results in part of the temporal retina of each eye projecting contralaterally instead of ipsilaterally, resulting in a contralateral projection that is too large and contains about 20° of the ipsilateral visual hemifield. As a result, the ipsilateral retinal projection is too small. The nasal retinal projection goes to the A layer in a normal pattern, the adjoining temporal retina goes to the A1 layer in a normal pattern of central to paracentral vision (but on the wrong side of the brain), and the rest of the temporal retina (the temporal extreme) projects normally to the ipsilateral A1 layer. The closely matching 1 and A segments of the A and A1 layers fuse, whereas the nonmatching 4 and C (left) and 3 and D (right) segments separate. The LGN projections to visual cortex either develop in a normal aligned pattern, as in the Midwestern type (left), or realign to form a continuous representation in visual cortex as in the Boston type (right). In the Midwestern type, projections from the medial parts of A and A1 are devoted to different parts of the visual field, and they could lead to neurons with two receptive fields and double vision. Fortunately, the A1 layer projection activates few neurons (smaller boxes in visual cortex). The normally innervated lateral segment of the A1 layer also activated few cortical neurons (possibly because of the common misalignment of the eyes). As a result of the suppression of the relay of the A1 layer to visual cortex, Siamese cats tested when viewing with only one eye are virtually blind in the ipsilateral hemifield. They also have no neural substrate for binocular vision and stereopsis). By realigning projections from the LGN to cortex, the Boston type has a larger functional visual field for each eye (e.g., K-3 or 11-C, rather than K-A or 11-1), but they also have no substrate for binocular vision. Most Siamese cats have a mixture of the two patterns.

it was uncertain how the abnormal retinal projections were produced because the gene allele that alters coat color and eye color could act in many ways to alter retinal projections. Most genes affect many traits, a phenomenon known as pleiotropy (Otto 2004). Fortunately, the key role of retinal pigment alone soon became apparent because coat and eye color are affected by a number of different genes.

At the time of Guillery's discovery, the University of Wisconsin maintained a breeding program for strains of domesticated mink with different coat colors (for the fur industry). Some of these mink had eye pigment but not coat pigment, and only mink with greatly reduced retinal pigment had abnormally large crossed retinal projections (Guillery et al. 1979; Sanderson et al. 1974). Other studies revealed that all mammals with a major reduction in retinal pigment have abnormal retinal projections, including a white tiger (Guillery and Kaas 1973), albino monkeys (Gross and Hickey 1980; Guillery et al. 1984), and human

albinos (Guillery et al. 1975). In addition, the size of the misprojection was found to be larger in albino cats, with no retinal pigmentation, than in Siamese cats, with greatly reduced retinal pigmentation (Creel et al. 1982; Pospichal et al. 1995).

In albino mammals, we now know that the normal retinal projections are a result of a defect in the tyrosinase gene, which produces the key enzyme in the synthesis of melanin pigment. Thus, the insertion of a functional tyrosinase gene into an albino strain of mice restores their ability to produce melanin and form normal retinal projections (Jeffery et al. 1994, 1997). It is not yet clear how the retinal pigment epithelium influences the developing neural retina, but it does alter the cell density of the retina (Jeffery et al. 1994) and the timing of when neurons in the temporal retina are generated (Dräger 1985; Reese et al. 1992). These differences could have the secondary effect of altering the projection pathways of retinal ganglion cells.

Question #2: How do the abnormal crossed retinal projections terminate in the LGN?

The abnormal retinal projections could form an orderly or disorderly projection pattern, and if orderly, several different retinotopic patterns might be possible. The question of how the retinal projections terminate was answered by recording from neurons in layer A1 to identify which parts of the retina must be visually stimulated to activate them, and by tracing the projections of ganglion cells from different parts of the temporal retina (Guillery and Kaas 1971). The answer was that the 20° vertical strip of temporal retina that misprojected contralaterally projected to the medial part of the A1 layer in a mediolateral pattern. Normally, this strip of retina projects ipsilaterally to the medial half of the A1 layer in a mediolateral pattern. The rest of the temporal retina projected normally to the lateral half of layer A1 in the ipsilateral LGN (Figure 3). This total pattern created a partial mismatch of the representations in layers A and A1 so that retinotopic information from each eye was no longer completely aligned in layers A and A1. The A layer, as in normal cats, represented the contralateral half of visual space from central vision to the temporal periphery (0-90°) in a mediolateral sequence, while the medial half of the A1 layer represented visual space in the opposite direction from 0° to 20° in the ipsilateral visual hemifield. This misalignment would appear to create a major visual impairment in Siamese cats; however, adjustments in cortex reduce the behavioral impact of the misdirected retinal projections.

The fusion of the medial parts of the A1 layer and the A layer is a direct consequence of them being innervated by the same eye and the role of waves of activity in the developing retina in the segregation of eye specific retinogeniculate projections (Torborg et al. 2005). For the same reason, the lateral and medial segments of layer A1 are separated (Kaas and Catania 2002).

Question #3: What happens when layers A and A1 project to visual cortex?

Normally, neurons in adjacent positions of layers A and A1 project to adjacent locations in primary visual cortex ($V1^{1}$), where the information is combined to produce neurons activated by both eyes, and binocular vision. Such neurons are activated by stimuli in nearly the same parts of visual space, and the small differences (disparities) in the receptive fields for each eye (the stimulating parts of visual space or the retina) allow for stereoscopic vision. Nobel laureates Hubel and Wiesel were the first to investigate what happens to the relay of layer A and layer A1 information to V1 of Siamese cats (Hubel and Wiesel 1971). These investigators found that V1 formed a continuous representation not only of the contralateral visual hemifield (as in normal cats), but also of the first 20° of the ipsilateral hemifield, with almost all of the activation based on the contralateral eye. Only a few patches of neurons in the part of V1 representing the temporal extreme (beyond 20°) of the contralateral hemifield responded to the ipsilateral eye, and these neurons were activated via the lateral normal segment of layer A1 of the LGN. Binocular neurons with nearly matching receptive fields were not found. The results indicated that the cortical projections from the abnormal segment of layer A1 did not project to V1 in register with the adjoining part of layer A1. Instead, they captured their own territory in V1, terminating in a reverse topographic pattern to extend the representation in V1 of the contralateral visual hemifield approximately 20° into the ipsilateral visual hemifield. Because Hubel and Wiesel studied Siamese cats in Boston, this type of cortical organization became known as the Boston pattern (Figure 3).

Another pattern of projections from the LGN to V1 of Siamese cats was soon apparent in my collaborative studies with Ray Guillery (Kaas and Guillery 1973). We found that the A1 layer projects in register with the A layer, to produce two superimposed mosaic-like representations of the visual field of the contralateral eye. The one representation based on the A layer proceeds from central vision to the temporal periphery of the contralateral visual hemifield, as in normal cats. The other representation proceeds from central vision to 20° into the ipsilateral visual hemifield, corresponding to the layer A1 segment that is abnormally innervated by the contralateral eye (Figure 3). However, only a few neurons were activated by this abnormal input. Thus, the relay of abnormal input was somehow "suppressed" in cortex. In addition, a few neurons were activated by inputs from the lateral segment of layer A1 with normal inputs from the ipsilateral eye. Yet a few neurons or neuron clusters were activated by mismatched inputs relayed from two locations in the visual field, via A and abnormal A1 layers. As these Siamese cats were studied in the Midwest, this pattern of cortical organization became known as the Midwestern pattern. Cooper and Blasdel (1980) found that many, perhaps most, Siamese cats have a mixed pattern of cortical organization so that parts of the cortical representation extended

into the ipsilateral hemifield, as reported by (Hubel and Wiesel 1971), and parts had abnormal inputs suppressed as we described.

As noted above, albino cats have a more extensive abnormal projection from the contralateral eye to the LGN than Siamese cats. In visual cortex of albino cats, investigators have reported that neurons form two overlapping inputs of either part of the contralateral visual hemifield, or the ipsilateral visual hemifield, each from the contralateral eye (Leventhal et al. 1985; Pospichal et al. 1995). Although little evidence has been reported for any substantial suppression of the relay of abnormal retinal inputs, abnormal inputs appear to activate separate clusters of neurons from those activated by normal inputs. Thus, individual neurons have seldom been activated by two different locations in the visual field. A similar result was obtained in an albino monkey (Guillery et al. 1984), and it appears that visual cortex of human albinos also may have two mirror-image, overlapping representations via the contralateral eye (Creel et al. 1974; Hedera et al. 1994; Morland et al. 2002; Schmitz et al. 2004). In contrast, the albino ferret largely reorganizes the relay of abnormal retinal input to form a single, extended map in visual cortex (Akerman et al. 2003). These differing outcomes indicate that the interaction of several conflicting tendencies in visual system development can result in quite different outcomes across species, and sometimes across individuals within a single breed (Kaas and Catania 2002).

Question #4: Are retinal projections to other brainstem targets also abnormal?

Although the LGN is the source of the most direct visual projection to cerebral cortex, and this projection underlies most of visual perception, other brainstem targets also receive projections from the retina, including the superior colliculus of the midbrain, the pretectal nuclei, and the nuclei of the accessory optic system. In albino and other mammals with a hypopigmented retina, all of these structures receive a larger than normal projection from the contralateral retina and a smaller than normal projection from the ipsilateral retina (Zhang and Hoffmann 1993), apparently reflecting a projection error similar to that observed in the LGN. The accessory optic system and the pretectal nuclei are involved in generating visuomotor reflexes, and the superior colliculus has an important role of using visual and other sensory information to help mediate eye and head movements so that gaze is oriented forward, toward objects of interest. Abnormal and defective visual reflexes, such as those generating a horizontal nystagmus, have been reported in albino mammals, including humans (Collewijn et al. 1985; Duke-Elder 1964; Guillery et al. 1984) and an albino monkey (Guillery et al. 1984), apparently as a result of abnormal projections to the accessory optic system (Zhang and Hoffmann 1993).

As for the retinal projections to the LGN, the temporal retina of Siamese cats projects abnormally to the contralateral rather than the ipsilateral superior colliculus (Kalil et al. 1971; Weber et al. 1978). The abnormal contralateral projection terminates in the rostral half of the superior colliculus, where ipsilateral projections from the temporal retina normally overlap contralateral projections from the nasal retina. Recordings from the superior colliculus of Siamese cats indicate that the two sets of inputs overlap each other while forming aligned mirror-image retinotopic maps, as they do in layers A and A1 of the LGN (Cynader and Berman 1972; Lane et al. 1974). However, few neurons respond to the anomalous retinal input. Thus, the misdirected inputs are largely suppressed. As a result, neurons are not responsive to inputs from separate, mirror-image locations in both hemifields of the contralateral eye. As in normal cats (Lane et al. 1974), Siamese cats also have a small, normal representation of the temporal retina of the contralateral eye. Siamese cats have abnormal visuomotor behavior (see below); however, investigators have not defined the role of the superior colliculus in these behaviors to date.

Question #5: How is vision altered in Siamese cats?

At first glance, the visual behavior of Siamese cats appears to be quite normal. They navigate in the environments quite well, avoid obstacles, and jump up onto surfaces. Yet these measures of visual behavior are rather crude. Several abnormalities in perception are suggested by the disruption of normal organization that occurs in visual cortex. First, there is almost no substrate for binocular vision because few neurons in visual cortex respond to both eyes, especially in the behaviorally important central 20° of vision, where almost all of the visual cortex activation is via the contralateral eye only. Thus, Siamese cats appear to lack stereoscopic depth perception (Packwood and Gordon 1975). In albino humans, neural mechanisms for global stereopsis appear to exist (Apkarian and Reits 1989), but they appear to depend on the relay of information from monocularly activated neurons in primary visual cortex to higher-order visual areas, where binocular neurons may occur (Zeki and Fries 1980).

Second, most Siamese cats suppress much of the relay of the abnormal projections from the temporal retina of the contralateral eye, which views the central 20° of the opposite hemifield. If we close one eye, we see most of the total visual field because of our extensive projection from the temporal retina. Because much or most of the smaller 45° projection from the temporal retina in cats (Figure 1) is suppressed in visual cortex of Siamese cats, they are virtually blind in the nasal hemifield when they view the world with one eye (Elekessy et al. 1973; Guillery and Casagrande 1977). This blindness is not apparent when both eyes are open. Although each eye sees only the temporal half of the visual field, the two eyes together see all of the visual field.

The lack of binocular interaction in visual cortex, however, means that the patterns of visual activation via each eye are independent, and there is no advantage in having the eyes aligned or no great cost to having them misaligned. Cross-eyed Siamese cats, which are common, might even benefit from having overlapping but independent views of a few degrees of frontal vision. As the Boston type of Siamese cat rearranges the relay of the abnormal projection in visual cortex, rather than suppressing it, these Siamese cats have a monocular visual field that extends 20° into the ipsilateral hemifield (Guillery and Casagrande 1977).

Other abnormalities of vision in Siamese cats are the result of reduced numbers of receptors and ganglion cells in the retina (Stone et al. 1978). Such lower cell densities may be responsible for other alterations in vision such as a decrease in visual resolution (Blake and Antoinetti 1976). In addition, as noted above, all abnormal projections to the accessory optic system, the pretectum, and superior colliculus likely disrupt vision.

Conclusions

The serendipitous discovery of an abnormal retinal projection in a Siamese cat by Ray Guillery in the late 1960s led researchers in a number of directions and to important discoveries. As a result, we have a better understanding of the following: (1) factors that affect the guidance of retinal axons to their proper targets in the brain, (2) how factors interact to create orderly representations of visual inputs in the visual cortex, and (3) how altered visual inputs affect visual behaviors. My role in some of these studies was also serendipitous because if I had not been investigating the normal organization of the visual system in a laboratory just down the hall from Ray Guillery, he would not have invited me to combine our skills and techniques in studies of the visual system of Siamese cats, an albino tiger, and an albino monkey. It was also fortunate that mink of different coat and eye pigmentation were available at the University of Wisconsin to help evaluate the role of eye versus coat pigmentation.

The scientific advances that resulted from the chance finding described above demonstrate the important role of luck; however, serendipity depends on more than luck. Ray Guillery was highly prepared to recognize an abnormality in the visual system of cats, and he was equally well prepared to grasp the significance of the abnormality and design a battery of experiments to reveal the full meaning of that abnormality. As in other fields, it seems that good things happen to those who work hard and are prepared. One reason for this apparent cause and effect relationship is that more research activity increases the chances that something unexpected will occur, and unexpected findings are those that open new doors. Research activity also prepares the mind for unexpected findings. One wonders how many important observations have been neglected because their significance was not appreciated.

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