Neuromorphological Plasticity

Gerald E. Schneider, PhD, Department of Psychology, Massachusetts Institute of Technology, Cambridge, MA 02139 (USA)

Brain Behav Evol 1973;8:91–109

Early Lesions of Superior Colliculus: Factors Affecting the Formation of Abnormal Retinal Projections; pp. 91–109

G.E.		Schneider
------	--	-----------

Department of Psychology, Massachusetts Institute of Technology, Cambridge, Mass.

Key Words

Development, brain
Hamster, Syrian (golden)
Plasticity, neuronal
Retinal projections
Superior colliculus
Thalamus, afferents
Visual function

Abstract

The longest fibers of the main optic tract reach the upper layers of the superior colliculus (SC) of the midbrain. Destruction of this terminal area in newborn hamsters caused striking anomalies in the distribution of the optic tract, studied after the animals were fully grown. Evidence of termination was found in areas normally devoid of such termination: in the remaining tissue of the colliculus and in the thalamic nucleus lateralis posterior (LP). An abnormally high density of termination was found in part of the ventral nucleus of the lateral geniculate body. These thalamic regions normally receive connections from SC. Retinofugal axons could also be induced to terminate in the medial geniculate body of the thalamus if the brachium of the inferior colliculus, which normally carries auditory information to this cell group, was ablated at birth together with the lesion of SC.

If the superficial layers of SC were destroyed unilaterally at birth, axons from the eye contralateral to the lesion not only reached the area of early damage, but also formed an abnormal decussation, crossing the tectal midline to terminate in the medial zone of the undamaged colliculus. Axons from the two eyes *competed for terminal space* in this intact colliculus, for they terminated in a nonoverlapping manner, and if the axons from the eye contralateral to the remaining SC were eliminated at birth, the anomalously recrossing axons increased in quantity and spread across the entire SC on the 'wrong' side of the midbrain. Hamsters with such an anomaly showed wrong-direction turning in response to visual stimuli in a large part of the visual field.

The less the amount of termination found in SC, the greater was the amount in LP. Thus, optic tract axons showed a '*pruning effect*' which may be attributed to a tendency for axons to conserve the quantity of their terminal arborizations. The pruning effect alone may account for the hypertrophy we found, after early SC lesions, of the dorsal terminal nucleus of the accessory optic tract. The tendency to invade vacated terminal space may be sufficient to account for an effect of early unilateral eye removal, namely, a pronounced increase in an ipsilateral retinal projection to the medial terminal nucleus of the accessory optic tract.

The greatest alterations in axonal projections were seen when the two effects, competition and pruning, seemed to act jointly. Additional factors may have to be considered in fully explaining such neuroplasticity; some of these have been suggested.

and the BIC, degenerating retinofugal axon terminals are found in this region as well as in LP (fig. 10F). The light-microscopic appearance of such degeneration is illustrated in figure 11. Electron microscope pictures of such a case, made of material prepared by R. KALIL and myself, confirm

the existence of degeneration in synaptic end-structures of axons of retinal origin (to be published).

20 other cases with lesions of the superior colliculus on the day of birth were studied in a similar manner. In 12 cases in which the large bundles of BIC fibers were found to be missing on one side, along with the superficial layers of the superior colliculus, a small area of retinofugal terminal degeneration was found in MGB, limited to the region illustrated in figure 10 but not extending as far from the optic tract. The early mid-brain damage in these cases did not include as many axons medial to the main bundles of BIC as in the case illustrated. In the remaining 8 cases, the BIC was clearly present, though usually somewhat reduced in size; in these cases, no evidence of a retinal projection to the MGB was found.

The availability of terminal space appears to be a necessary factor for the occurrence of the anomalous connection. We do not yet know whether it is sufficient, for the connection may occur only when the axons cannot find normal terminal space in the superior colliculus.

*Retinal Projection to the Wrong Side of the Midbrain:
Competition between Axon Populations for Terminal Space*

A different experimental test for the significance of a 'competition for terminal space' I reported at a recent meeting of the American Association of Anatomists [SCHNEIDER, 1971]. The experiment was made possible by a phenomenon regularly seen in cases of unilateral early lesions of the superior colliculus. As illustrated in figure 6, some retinofugal axons form an abnormal decussation over the tectal midline. The projection from the retina to the superficial gray of the colliculus is normally a totally crossed one, but in these cases, some axons which reach the damaged right colliculus, having crossed once at the optic chiasm, recross the midline and pass into the undamaged left colliculus. Thus, axons from two eyes are going into the same superficial gray layer of the left colliculus. Do they compete for terminal space?

To answer this question, the first step was to look at the projections of the two eyes separately, to see whether they terminate in an over-

lapping manner, or instead exclude each other from their respective regions of termination. The next step was to see how the abnormally re-crossing fibers are affected when the fibers from the other eye, the ones normally innervating the undamaged colliculus, are removed. If axons from the two eyes compete for terminal space, the distribution of the re-crossing fibers should be increased by the removal of their competitors. 14 animals, from 3 litters, were operated on the day of birth. A lesion of the right superior colliculus was inflicted in every case. In 6 of these cases, the right eye was removed at the same time. After behavioral testing in adulthood, the left eye was removed in 13 cases, and after a survival period of 5 more days, the brains were prepared for staining as described. The opposite, right eye was removed in the remaining case, in which only the right colliculus had been damaged at birth.

The results can be illustrated by charts of degenerating axons and terminals in sections through the middle of the superior colliculus in typical cases. Figure 12 illustrates two cases in which the lesion at birth was confined to the right colliculus, both eyes remaining intact. When the projections of the left eye were studied in the adult (fig. 12, left), axons could be followed to the surface of the damaged right colliculus, with some subjacent termination. The axons which recrossed into the wrong colliculus were found to terminate only in a medial zone of the superficial gray layer, extending over the whole rostro-caudal extent of the structure except for the most anterior levels. In another, similar case the projections of the right eye (fig. 12, right) were found to terminate in a normal manner in the superficial gray of the left colliculus, except for a striking absence of termination in a medial zone corresponding closely to the zone of abnormal innervation described for the previous case. The photographs in figure 13 illustrate the sharp line between these zones innervated by separate eyes; this line was often, but not invariably, oriented perpendicular to the tectal surface. The degeneration in the medial zone showed a fairly normal pattern, with some patches of extra density in the deeper part of the superficial gray.

Thus, axons from the two eyes do not terminate in an overlapping manner; rather, they appear to exclude each other. The abnormally crossing axons appear to be 'stopped' by the fibers from the other eye. The crucial test of the hypothesis of competition for terminal space was to see how the spread of these axons is affected by elimination of the fibers from the other eye. Figure 14 shows a chart corresponding to the previous ones, except that it is from a case in which the lesion at birth included

Fig. 12. Charts of silver-stained coronal sections through the superior colliculus of two hamsters in which the superficial layers on the right side were destroyed on the day of birth. Axonal and terminal degeneration are indicated with dashed lines and dots. Left: case 20-5 in which the left eye was removed in the adult animal, 5 days before sacrifice. Right: case 20-4, treated similarly except that the right eye was removed in the adult. From SCHNEIDER [1972].

Fig. 13. Photomicrographs illustrating the sharp line between the areas of projection of the two eyes in the superficial gray layer of the left superior colliculus in cases where the right side was damaged on the day of birth. Tectal surfaces are at the top. Left: from case 20-5, section charted in figure 12. Middle: from case 20-2, treated similarly, but where the line is not perpendicular to the surface. Right: from case 20-4, section charted in figure 12. Fink-Heimer stain. X 183.

Fig. 14. Chart of coronal section through the superior colliculus of hamster case 21-1, in..which the lesion on the day of birth included the right eye as well as the right tectum. The remaining left eye was removed in the adult. As in the case illustrated in figure 12 (left), the axons from the left eye have crossed in the optic chiasm and reached the damaged right colliculus; many recross the tectal midline and are distributed in the superficial gray layer on the 'wrong' side. From SCHNEIDER [1972].

both the right colliculus and the right eye. The axons from the remaining left eye follow a course similar to that in the previous case, but with a dramatic difference in the anomalous decussation. The bundle of recrossing axons is increased in size (see also fig. 15), and it terminates throughout the extent of the superficial gray layer of the left ('wrong') colliculus, though it becomes quite sparse laterally, where the superficial gray layer appears shrunken, apparently as a result of transneuronal atrophy. The anomalous bundle is obvious upon gross inspection of the brain after the cerebral hemispheres have been dissected away (fig. 16). The recrossing axons form a large fasciculus, the anterior edge of which is caudal to the anterior third of the undamaged colliculus, so that axons which pass to the anterior part of the left colliculus have to turn rostrally after crossing the midline.

Fig. 15. Superior colliculus, mid-rostral level, of adult hamster case 21-4, in which the surgery on the day of birth consisted of a heat lesion of the right tectum and removal of the right eye. The anomalous bundle of recrossing retinofugal axons is very conspicuous. Coronal section chosen to match the ones in figures 2 and 3. Loyez stain for myelin. X24.

Fig. 16. The anomalous bundle of axons of retinal origin which recross at the tectal midline is conspicuous in this photograph of the brainstem of case 21-1. (A chart of a section from this case is shown in fig. 14.) The hemispheres have been dissected away, and the brain is arranged so the tectal surface is normal to the line of view of the camera. The anomalous bundle is indicated by an arrow in a matching drawing at the right. Millimetric grid in background.

In control cases, only one eye was removed at birth, and the projections of the other eye were studied in adulthood. In the colliculus, the ipsilateral projection, which is normally found only in the stratum opticum of the anterior part, was somewhat increased, with axons invading certain patches of the superficial gray layer in the somewhat shrunken tectum. This projection cannot account for the results in the cases with recrossing fibers.

The experiments described confirm the reality of the phenomenon of 'competition for terminal space', demonstrating the tendency of the retino-fugal axons to occupy vacant terminal space in a manner excluding at least other retinofugal axons. In a series of 14 cases, only 3 showed exceptions to the patterns described. In 1 of the 8 with only the right colliculus damaged at birth there were no recrossing axons; in this case a small medial part of the superficial gray layer had been spared; in a second case with an exceptionally deep lesion, the number of recrossing axons was very small. In 1 of the 6 with lesions of both right colliculus and right eye, few axons crossed.

Function of the Anomalous Retinotectal Pathway to the Wrong Side of the Brain

If the abnormally recrossing fibers are functional, and if activity in the retinotectal axons can control orienting movements independent of other retinofugal pathways, one would predict that animals with the abnormal decussation would show visually elicited turning in the wrong direction (assuming that the tectal efferents to the motor system maintain their normal organization). The prediction has been shown to be valid.

In testing the animals described in the previous section, ALFREDO SAD-UN and I observed visually elicited head turning in response to hand-held sunflower seeds. The 5 animals with extensive retinal projections to the wrong side of the midbrain showed turning in the wrong direction when seeds were presented in the temporal visual field of the remaining left eye, and correctly directed turns in response to presentations in the more nasal field. In these cases, we encouraged misdirected turning by rewarding the animals on the side opposite to that of the visual stimulus. We compared this behavior, in a 'blind' testing procedure, with that of one-eyed matched control animals, and found that the experimental animals could reliably be distinguished on the basis of their turning responses alone.

Subsequently, DAVID SINGER and I have tried to refine the food perimeter procedure systematically using videotape recording followed by

Fig. 17. Results of videotape analysis of the left visual field in case 32-5, in which the right eye and the superficial layers of the right superior colliculus were ablated at birth. The hamster's eye is shown at the center of a sphere representing the visual field; grid lines are 20° apart, with extra lines at horizontal eye level and at 90° from the straight ahead. Open circles represent positions of the stimulus in the field where turns in the correct direction were elicited. Black squares represent turns in the wrong direction. Circles inside squares represent 'ambivalent' turns.

slow-motion analysis. We are now able to restrict the visual stimuli to small regions of the visual field, measured on coordinates with respect to the animal's head. Also, we have been able to train animals to hold their heads relatively motionless during tactile fixation of a small raised hole where seeds are occasionally presented. An overhead camera and a camera to one side record the movements of the animal and the position of the stimulus object - a small black rubber sphere (diameter 1.2 cm) upon which a sunflower seed is stuck, at a distance of about 14 cm from the animal's head. Turns in the wrong direction occur, in animals with retinofugal axons going to the wrong side of the midbrain, even when the animals were not previously rewarded on the wrong side.

With strict criteria for judging genuine visually elicited responses, we have obtained maps of the visual field like that shown in figure 17. The exact position and extent of the 'wrong-way turning field' does vary

somewhat, but in most such cases turns in the abnormal direction result from presentations restricted to the upper temporal part of the field, whereas correct-direction turns follow stimuli in the lower nasal regions. Along the border between these two sectors of the field we often observe a peculiar ambivalent turning, in which a turn in one direction rapidly reverses itself to the opposite side. At present, we are uncertain to what degree eye movements may contribute to the overlap between the normal and abnormal fields.

We have also begun quantitative assessments of the extent as well as the direction of the head movements. We have found, for the animals with the early lesions, that as the stimulus is moved more and more temporally in the visual field, the wrong-direction responses do not increase in extent as correct responses do in normal animals. The difference suggests that the retinal fibers going to the wrong side of the brain do not terminate in a topographic order corresponding to the normal retinotopic map.

Comments on 'Terminal-Space' Availability

Figure 18 illustrates diagrammatically the concept of competition for terminal space, or a tendency for axons to fill or invade available or vacated terminal space, demonstrated by the experiments just described. Two hypothetical structures are indicated, each innervated from two sources, but the terminal distribution of one is limited by the presence of the other. This effect is demonstrated by the consequence of removing one of the sources of input to each structure: the other system then expands its terminal field.

Fig. 18. Diagrammatic illustration of the concept of competition for terminal space, or a tendency for axons to invade available or vacated terminal space.

I deliberately avoid the term 'synaptic space' which is too specific for describing these results. There may be few or no synapses formed at the time when the abnormal distribution of axons occurs. (The dynamics of development have not yet been studied.) The competition appears to be *between* different axon populations for some kind of space, not necessarily defined by available postsynaptic sites. It is possible that the critical space is defined by chemical factors, produced by the axons or by denervated membranes, or both; but such chemical factors should *not* be considered as *specific* to a single cell group.

The Pruning Effect: Compensatory Sprouting is a Separate Factor

A factor influencing the formation of anomalous projections separate from the factor of terminal space availability was first suggested to me by recalling something I learned from my father, a tree surgeon. If the upper branches of a growing tree are pruned, the lower branches show a compensatory increase in growth. (The effect appears to vary with the age and the species of tree.) Could axonal 'trees' in the brain show a similar effect? (We might expect a similar variation with age and 'species' or cell type!) Experimental demonstration requires that terminal space be held constant and the 'pruning' varied. This is just what, in effect, we have in the group of animals described above in the study of retinotectal axons which pass to the wrong side of the brain. In all these animals the superficial layers of the right superior colliculus (SC) were largely or completely destroyed on the day of birth. In 13 cases, such removal of a major region of optic tract termination led to an anomalous termination of optic tract fibers in the right LP, and also (in most cases) caused the optic tract to establish connections with the 'wrong' left colliculus. The anomalous termination in the undamaged colliculus was much greater in extent in 5 of the 6 cases in which the right eye had also been removed at birth. Therefore, we have two groups of animals which we can assume have equivalent terminal space in LP vacated by the removal of tectothalamic fibers, but are known to have very different amounts of optic tract termination in the tectum. Is the amount of termination in LP greater in the animals with less termination in the colliculus? An affirmative answer is indicated by the results of a procedure for estimating the volume of terminal degeneration in both of these structures.

To obtain the required quantification, we projected each silver-stained

Fig. 19. Graph of the volumes of terminal degeneration in the 'wrong' superior colliculus (abscissa) and of the densest terminal degeneration in the nucleus lateralis posterior (ordinate). Numbers are area sums, in thousands of mm^3 , over all sections spaced at about 170 μm intervals in the original brains, projected X 150. *rSC(0)*: cases with lesions of the right superior colliculus on the day of birth. *rSCrEE(0)*: cases with the same lesion, but also a right eye enucleation on the day of birth.

section from a regularly spaced series at a magnification of X 150, and outlined the areas of dense terminal degeneration (fig. 7), confirmed by high-power scanning with the light microscope. The areas were measured with a planimeter or by counting grid squares, and summed for each structure in each case; the sums are proportional to the estimated volumes in which the terminal degeneration is enclosed. The procedure for LP was carried out without knowledge of results for SC. Results obtained by one observer (myself) are shown graphically in figure 19; similar group differences were obtained independently by two other observers, using slightly different criteria. The abscissa, using an uncorrected scale, shows values proportional to the volume of terminal degeneration in the superior colliculus. (Only the 'wrong' SC was measured; the volume of terminal degeneration in the damaged SC was comparatively small, and not always easy to distinguish from degeneration in the pretectal area.) The ordinate shows values proportional to the volume of only the very dense terminal degeneration in the nucleus lateralis posterior. Each point shows the re-

Fig. 20. Diagrammatic illustration of the concept of a tendency for axons to conserve at least a minimum quantity of terminal arborization, or the 'pruning effect'.

suiting values for one animal. Values for 2 normal animals, without early lesions, are included. In these cases, the values for SC are for the entire superficial gray layer on one side.

The results clearly indicate that the amount of terminal degeneration in LP is inversely proportional to the amount in SC. This finding provides evidence for a factor important in the formation of altered axonal connections, separable from the factor of terminal-space availability. It might be called a tendency to conserve at least a minimum quantity of terminal arborization, but I shall call it the 'pruning effect' for short. The concept is illustrated in figure 20.

On the Relative Roles of the Two Factors

It seems reasonable that altered axonal connections might be more likely or greater in quantity when both factors discussed above (fig. 18, 20) are active. After early lesions of the superficial layers of the superior colliculus, both factors could influence the formation of the increased or novel retinofugal projections to the ventral nucleus of the lateral geniculate, LP, MGB, and the remaining tectum. However, there is some evidence that these factors can sometimes act in isolation from each other.

An independent action of the 'pruning effect' is suggested by observations of superinnervation of areas in which no terminal space has been

vacated. This appears to be the case for the dorsal terminal nucleus of the accessory optic tract (DTN), which, shows a striking hypertrophy when the tectum on the same side is damaged at birth (fig. 6). The enlargement causes the nucleus to merge caudally with the lateral terminal nucleus, from which it is normally separated. Rostrally it merges with the nucleus of the optic tract somewhat more obviously than in a normal case. After eye removal in the adult, terminal degeneration of normal density can be stained throughout the region. An increase in terminal space appears to be effected by a hypertrophy rather than by the removal of afferents, since DTN has been found to receive few, if any, connections from the superior colliculus or pretectal region in the hamster (unpubl. observations).

The influence of terminal space availability on the formation of altered optic tract connections, independent of any pruning effect, is demonstrated for hamsters in experiments other than those described. The medial terminal nucleus of the accessory optic tract (MTN) normally receives a dense projection from the contralateral eye, while the contribution from the ipsilateral eye appears to be negligible in quantity. Only a few scattered degenerating axons can be traced into this nucleus on the ipsilateral side. However, if the contralateral eye has been removed early in life (I have done this in otherwise intact animals on the day of birth and on days 1, 2 and 8 as well as in combination with ipsilateral tectum ablation) the ipsilateral projection field blooms into a conspicuous region of dense termination. The most likely explanation is a sprouting of the ipsilateral afferents, although the possibility of sprouting or misrouting of fibers at the optic chiasm cannot be ruled out. We can trace the optic tract to MTN days before the age at which removal of one eye can still result in this change. Other regions where axons from the ipsilateral eye terminate do not show such clear changes in the cases of unilateral eye removal on day 8. However, after such surgery on day 0—2, there is evidence of an increased ipsilateral optic tract, with an increased terminal field in the ventral nucleus of the lateral geniculate body, and probably elsewhere. Quantitative analysis of these and further cases will be undertaken.

The notion of competition for terminal space (often specified as synaptic space) or invasion of vacant terminal space, has become a dominant one in neuroplasticity paradigms, providing an important supplement to studies of replacement-type regenerative growth. Most reports have concerned the anatomical sequelae of lesions in adult animals - see other

papers in this volume, also the introduction to the present paper. Recent reports of the effects of early lesions have provided examples of anomalies in axonal connections in species other than the hamster. KALIL [1972] has reported that early removal of one eye in kittens leads to sprouting of anomalous connections in the dorsal nucleus of the lateral geniculate body (LGd). The invasion of vacated terminal space proceeds in isolation from pruning effects (but it is uncertain whether the sprouting is accompanied by some reduction in termination of the axons elsewhere). LUND [1972; this volume] has described a similar experiment in rats, in which he obtained alterations in the ipsilateral retinotectal connections. CUNNINGHAM [1972] has repeated and extended the work of GOODMAN and HOREL [1966] on the effects of posterior neocortex ablations on retinal projections in the rat. Aftgf; early as well as later lesions, he found not only an increased optic tract termination in the ventral nucleus of the lateral geniculate and in the pretectal area but also a projection to LP -all areas partially denervated by the cortical lesion. In addition he observed a hypertrophy of the pretectal region, possibly due to the 'pruning' of axon terminals by the degeneration of LGd. In a similar experiment in the hamster [SCHNEIDER, 1970] the only identifiable anomaly seen after early posterior-cortex lesions was in the laminar arrangement of terminals in SC. The factors responsible for this species difference have not been specified. Cortex lesions can also lead to alterations in connections of otherjgortical regions, as demonstrated in work reported by LYNCH and COTMAN [1972]. Removal of entorhinal input to the hippocampus, in young or in older rats, caused striking changes in the termination patterns of other hippocampal afferents.

HICKS and D'AMATO [1970] have reported an altered axonal pathway that is difficult to explain only in terms of the factors suggested above, for it involves the dynamics of decussation [cf. LUND, 1972]. In their experiment, early hemispherectomy in the rat led to the appearance of uncrossed pyramidal tract axons originating in the remaining hemisphere.

In the neuroplasticity literature, the 'pruning effect' has not generally been considered. Studies of regeneration, for example, have concentrated on growth at the cut ends of axons, and have neglected possible changes at more proximal points along the fibers. An exception is RAMON Y CA-JAL'S [1928] consideration of the effects of cerebellar and neocortical lesions. His preparations revealed that axons whose end branches had been severed could show a hypertrophy of more proximal collateral branches. He reviewed similar findings by other investigators.

Notes for a Theory of Plasticity of Axonal Connections

Neuroplasticity studies have generally stressed the finding of reliable examples of altered connections, rather than the testing of possible mechanisms. As in the case of many ill-understood biological phenomena, so in neuronal plasticity the multiplicity of possible determining factors can seem staggering. Nevertheless, perhaps we have enough information to suggest an outline for a theory, if only to have a scaffolding for the development of better understanding. One might consider that the first question to be asked should concern the possible stimuli for abnormal axonal growth. However, it could be suggested that if axons are in a 'growth state', sending out filopodia to 'feel the terrain', as is more likely to be the case for the neonatal animal than for the adult, no special stimulus for anomalous growth would be needed. Thus, we could postulate that the axons of the optic tract are in such a growth state during at least the first 5 days of a hamster's life (and probably much longer), even after they have grown into the superior colliculus. If the colliculus is damaged, the axons regrow into the tectum, terminating in the available 'space'. If the space is greatly restricted, the axons sprout collaterals in the thalamus (in LP), not necessarily because the degenerating tectothalamic fibers produced some stimulus which induced collateral sprouting, but perhaps only because terminal space (of the proper kind?) was available there for the 'searching' axons. In any case, we are ignorant of the nature of any special stimuli which cause abnormal growth, so I have omitted further discussion of this issue.

To indicate the speculative nature of the illustration, it should be pointed out that we have no certain information concerning the time of arrival of the last of the retinotectal axons, though at least the first ones appear to have distributed themselves over the SC by the time the animal is 1 day old (unpubl. anterograde degeneration experiments). Also, we do not know whether a single axon could sustain collaterals in both SC and LP.

An understanding of the mechanisms of plasticity of axonal connections will probably develop along with neuroembryological theories of axonal growth and synaptogenesis. Much like the behavior of whole organisms, the behavior of cells is determined by both endogenous and exogenous factors. What follows is essentially a list of suggested factors, separated into endogenous and exogenous (intrinsic and extrinsic to neurons), which will have to be considered in explaining neuroplasticity effects, and

species differences in these effects. The list is severely narrowed by elimination of many important but indirect factors, including those affecting the phenomena of retrograde and transneuronal degeneration and atrophy. Also neglected are the phenomena of dendrite growth and plasticity [MOREST, 1969; VATJVERDE, 1968,1971].

The 'pruning effect' appears to be due to an intrinsic tendency of the neuron to conserve the amount of its axonal arborizations. This tendency, and other factors affecting plasticity, may vary with the cell type, axon type, or with intrinsic biochemical features. Another factor is the age of the cell, and the correlated internal changes associated with the growth of its processes and the formation of synaptic connections; extrinsic influences also change with age, e.g. whatever influences are due to the presence of myelin. The theoretical considerations of ALTMAN [1970] and JA-COBSON [1970] have stressed the factors of cell type and age. A related factor is the timing of growth or regeneration of axons: this might be expected to be crucial in determining the ability of the axon to compete for terminal space, although even when such competition occurs it may not be true that vacant space is filled on a 'first come, first served' basis. Other factors in the dynamics of growth may also prove important, e.g. the properties of the growth cone [MOREST, 1968] could influence the rate, direction and spacing of growing and sprouting axons. Endogenous factors in cells (pre- or postsynaptic) could determine synaptic density, or synapse type [LUND and LUND, 1971; MUGNAINI, 1970]. There may even be an ongoing turnover of synapses and synaptic end-structures in normal brain tissue [SOTELLO and PALAY, 1971; MOORE *et al*, 1971] that could vary from site to site.

Extrinsic factors include trophic effects of neuronal activity on axons and their terminals [CRAGG, 1972]. However, whatever trophic effects actually occur might be constrained by competitive interactions between adjacent axonal endings and by a conservation of terminal quantity by single neurons. Other extrinsic factors involve cell-cell and cell-substrate interactions. Competition between axons for terminal space, or more simply a tendency to grow into and occupy vacant terminal space, is such a factor, which may have to be subdivided according to the agents determining the critical 'space'. Thus, there may be chemical agents, not specific to axon type or perhaps specific to certain classes of axons, which broadcast locally the availability of terminal space. Chemical factors may be more specific in nature, e.g. growth of axons could be guided by chemotaxis, and their termination by specific chemoaffinities [SPERRY, 1963, 1971; re-

views by JACOBSON, 1970; GAZE, 1970], but demonstrations of chemospecificity effects have not been as direct as one might wish. Another factor could be the presence of satellite cells, which could limit or otherwise alter the plasticity of connections. A complex factor may involve interactions within a population of axons such that they arrange themselves in a certain order in their terminal region. Evidence for such a possibility comes from work on the development of the retinotectal projection in *Xenopus* [GAZE *et al.*, 1972] and from work on the regeneration of this projection in goldfish [SHARMA, 1972a, b, c; YOON, 1971, 1972a, b; cf. the review and discussion by GAZE, 1970].

In this paper, I have tried to convince you of the reality of two of these factors, illustrated in figures 18 and 20. Their relative roles are only partly known for the system under investigation. The roles of other factors are less certain, but some at least seem approachable by currently available experimental means.

Acknowledgements

I thank W. J. H. Nauta and H. L. Teuber, for frequent encouragement and advice; C. Kerr, S. Jhaveri, and I. Winzer for assistance with the major histology; D. Singer and A. Sadun for collaboration in the behavioral testing; S. J., W. J. H. N., and H. L. T. for criticism of the manuscript, and L. Snover for typing.

References

- ABPLANALP, P.: Some subcortical connections of the visual system in tree shrews and squirrels. *Brain, Behav. Evol.* 3: 155-168 (1970).
- ALTMAN, J.: Postnatal neurogenesis and the problem of neural plasticity; in HXM-WICH *Developmental neurobiology*, pp. 197-237 (Thomas, Springfield 1970).
- ALTMAN, J. and CARPENTER, M. B.: Fiber projections of the superior colliculus in the cat. *J. comp. Neurol.* 116: 157-178 (1961).
- CAMPOS-ORTEGA, J. A.; HAYHOW, W. R., and CLUVER, P. F. DE V.: A note on the problem of retinal projections to the inferior pulvinar nucleus of primates. *Brain Res.* 22:126-130 (1970).
- CASAGRANDE, V. A.; HALL, W. C., and DIAMOND, I. T.: Formation of anomalous projections from the retina to the pulvinar following removal of the superior colliculus in neonatal tree shrews. *Progr. and Abstr., Soc. for Neuroscience*, 2nd Annu. Meet., Houston 1972, p. 231.
- CRAGG, B. G.: Plasticity of synapses; in BOURNE *The structure and function of nervous tissue*, vol. 4, pp. 1-60 (Academic Press, New York 1972).

- CUNNINGHAM, T. J.: Sprouting of the optic projection after cortical lesions. *Anat. Rec.* 172: 298 (1972).
- FINK, R. P. and HEIMER, L.: TWO methods for selective silver impregnation of degenerating axons and their synaptic endings in the central nervous system. *Brain Res.* 4: 369-374 (1967).
- GAZE, R. M.: The formation of nerve connections (Academic Press, New York 1970).
- GAZE, R. M.; CHUNG, S. H., and KEATING, M. J.: Development of the retinotectal projection in *Xenopus*. *Nature new Biol.* 236: 133-135 (1972).
- GOODMAN, D. C. and HOREL, J. A.: Sprouting of optic tract projections in the brain stem of the rat. *J. comp. Neurol.* 127: 71-88 (1966).
- HALL, W. C. and EBNER, P. F.: Parallels in the visual afferent projections of the thalamus in the hedgehog (*Paraechinus hypomelas*) and the turtle (*Pseudemys scripta*). *Brain, Behav. Evol.* 3: 135-154 (1970).
- HAMORI, J.: Presynaptic-to-presynaptic axon contacts under experimental conditions giving rise to rearrangement of synaptic structures; in VON EULER, SKOGLUND, and SODERBERG Structure and function of inhibitory neuronal mechanisms, pp. 71-80 (Pergamon Press, New York 1968).
- HAYHOW, W. R.; WEBB, C. and JERVIE, A.: The accessory optic fiber system in the rat. *J. comp. Neurol.* 115: 187-215 (1960).
- HEDREEN, J. C.: Diencephalic projection of the retina in the cat. *Anat. Rec.* 166: 317 (1970).
- HEIMER, L. and PETERS, A.: An electron microscope study of a silver stain for degenerating boutons. *Brain Res.* 8: 337-346 (1968).
- HICKS, S. P. and D'AMATO, C. J.: Motor-sensory and visual behavior after hemispherectomy in newborn and mature rats. *Exp. Neurol.* 29: 416-438 (1970).
- JACOBSON, M.: Developmental neurobiology (Holt, Rinehart & Winston, New York 1970).
- KALIL, R. E.: Formation of new retino-geniculate connections in kittens after removal of one eye. *Anat. Rec.* 172: 339-340 (1972).
- Liu, C.-N. and CHAMBERS, W. W.: Intraspinal sprouting of dorsal root axons. *Arch. Neurol. Psychiat.* 79: 46-61 (1958).
- LUND, R. D.: Anatomic studies on the superior colliculus. *Invest. Ophthalm.* 11: 434-441 (1972).
- LUND, R. D. and LUND, J. S.: Synaptic adjustment after deafferentation of the superior colliculus of the rat. *Science* 171: 804-807 (1971).
- LYNCH, G. S. and COTMAN, C. W.: Neuronal adjustments in the hippocampus following lesions of the entorhinal cortex. *Progr. and Abstr., Soc. for Neuro-science*, 2nd Annu. Meet., Houston 1972, p. 239.
- MARTIN, G. F.: Efferent tectal pathways of the opossum (*Didelphis virginiana*). *J. comp. Neurol.* 135: 209-224 (1969).
- MCCOUCH, G. P.; AUSTIN, G. M.; LIU, C. N., and Liu, C. Y.: Sprouting as a cause of spasticity. *J. Neurophysiol.* 21: 205-216 (1958).
- MOORE, R. Y.; BJORKLUND, A., and STENEVI, U.: Plastic changes in the adrenergic innervation of the rat septal area in response to denervation. *Brain Res.* 33: 13-35 (1971).

- MOREST, D. K.: Identification of homologous neurons in the posterolateral thalamus of cat and Virginia opossum. *Anat. Rec.* 151: 390 (1965).
- MOREST, D. K.: The growth of synaptic endings in the mammalian brain. A study of the calyces of the trapezoid body. *Z. Anat. EntwGesch.* 127: 201-220 (1968).
- MOREST, D. K.: The growth of dendrites in the mammalian brain. *Z. Anat. EntwGesch.* 128: 290-317 (1969).
- MUGNATNI, E.: The relation between cytogenesis and the formation of different types of synaptic contact. *Brain Res.* 17:169-179 (1970).
- NAUTA, W. J. H. and EBBESSON, S. O. E.: Contemporary research methods in neuroanatomy (Springer, New York 1970).
- RAISMAN, G.: Neuronal plasticity in the septal nuclei of the adult rat. *Brain Res.* 14: 25-48 (1969).
- RAMON Y CAJAL, S.: Degeneration and regeneration of the nervous system; vol. 2. Trans. MAY, R. M. (Hafner, New York 1968; reprint of 1928 edition).
- SCHNEIDER, G. E.: Superior colliculus and visual cortex: contrasting behavioral effects of their ablation in the hamster; Ph. D. Diss., MIT, Cambridge (1966).
- SCHNEIDER, G. E.: Contrasting visuomotor functions of tectum and cortex in the golden hamster. *Psychol. Forsch.* 31: 52-62 (1967).
- SCHNEIDER, G. E.: Retinal projections characterized by differential rate of degeneration revealed by silver impregnation. *Anat. Rec.* 160: 423 (1968).
- SCHNEIDER, G. E.: Two visual systems. Brain mechanisms for localization and discrimination are dissociated by tectal and cortical lesions. *Science* 163: 895-902 (1969).
- SCHNEIDER, G. E.: Mechanisms of functional recovery following lesions of visual cortex or superior colliculus in neonate and adult hamsters. *Brain, Behav. Evol.* 3: 295-323 (1970).
- SCHNEIDER, G. E.: Competition for terminal space in formation of abnormal retino-tectal connections, and a functional consequence. *Anat. Rec.* 169: 420 (1971).
- SCHNEIDER, G. E.: Development and regeneration in the mammalian visual system; in EDDS, BARKLEY, and FAMBROUGH Genesis of neuronal patterns. *Neurosci. Res. Prog. Bull.* 10: 287-290 (1972).
- SCHNEIDER, G. E. and NAUTA, W. J. H.: Formation of anomalous retinal projections after removal of the optic tectum in the neonate hamster. *Anat. Rec.* 163: 258 (1969).
- SHARMA, S. C.: Reformation of retinotectal projections after various tectal ablations in adult goldfish. *Exp. Neurol.* 34:171-182 (1972a).
- SHARMA, S. C.: Restoration of the visual projection following tectal lesions in goldfish. *Exp. Neurol.* 35: 358-365 (1972b).
- SHARMA, S. C.: Redistribution of visual projections in altered optic tecta of adult goldfish. *Proc. nat. Acad. Sci., Wash.* 69: 2637-2639 (1972c).
- SOTELO, C. and PALAY, S. L.: Altered axons and axon terminals in the lateral vestibular nucleus of the rat. *Lab. Invest.* 25: 653-671 (1971).
- SPERRY, R. W.: Chemoaffinity in the orderly growth of nerve fiber patterns and connections. *Proc. nat. Acad. Sci., Wash.* 50: 703-710 (1963).
- SPERRY, R. W.: HOW a developing brain gets itself properly wired for adaptive function; in TOBACH, ARONSON, and SHAW The biopsychology of development, pp. 27-44 (Academic Press, New York 1971).

- SUMI, S. M. and HAGER, H.: Electron microscopic study of the reaction of the newborn rat brain to injury. *Acta Neuropath.* 10: 324-335 (1968).
- TARLOV, G. E. and MOORE, R. Y.: The tecto-thalamic connections in the brain of the rabbit. *J. comp. Neurol.* 126: 403-422 (1966).
- TEUBER, H.-L.: Mental retardation after early trauma to the brain: some issues in search of facts; in ANGLE and BERING Physical trauma as an etiological agent in mental retardation, pp. 7-28 (US Dept. of Health, National Institutes of Health, Bethesda 1970).
- VALVERDE, F.: Structural changes in the area striata of the mouse after enucleation. *Exp. Brain Res.* 5: 274-292 (1968).
- VALVERDE, F.: Rate and extent of recovery from dark rearing in the visual cortex of the mouse. *Brain Res.* 33:1-11 (1971).
- YOON, M.: Reorganization of retinotectal projection following surgical operations on the optic tectum in goldfish. *Exp. Neurol.* 33: 395-411 (1971).
- YOON, M.: Reversibility of the reorganization of retinotectal projection in goldfish. *Exp. Neurol.* 35: 565-577 (1972a).
- YOON, M.: Transposition of the visual projection from the nasal hemiretina onto the foreign rostral zone of the optic tectum in goldfish. *Exp. Neurol.* 37: 451-462 (1972b).