CONTROL OF CELL NUMBER IN THE DEVELOPING MAMMALIAN VISUAL SYSTEM

BARBARA L. FINLAY and SARAH L. PALLAS*  
Department of Psychology and Section of Neurobiology and Behavior, Cornell University, Ithaca, NY 14853, U.S.A.
*Present address: Department of Brain and Cognitive Sciences, E25-618, M.I.T., Cambridge, MA 02139, U.S.A.

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1. INTRODUCTION

Cells are the fundamental units for the organization and transmission of information in the nervous system. The number and density of photoreceptors limits the brain with which the visual world can be sampled. The inescapable limitation imposed by cell number and related processing capacity constrains the form of the visual system and the nature of visually guided behavior. For example, Hughes (1977) has calculated that if the ganglion cell density of the entire cat retina was the same throughout as the peak of cell density in its area centralis, and the visual cortex were also proportionately increased, the visual cortex (area 17) of the cat would have to be five times larger than the human visual cortex. Rather than processing high resolution views of the visual world in parallel, with a uniformly high receptor density, high resolution views of the visual world in animals specialized for high-acuity vision are processed serially using head, eye and body movements for successive fixations. The evolution of the neural machinery for producing, processing and comparing successive views of the world through eye movements can be thought of as a consequence of the constraints imposed by limitations of cell number and processing capacity. The nature of cellularly economical ways of organizing visual information is clearly important for understanding the paths of visual system evolution.

Cell number in the visual system must also be understood in terms of the more general constraints on cell number in the entire developing vertebrate brain (Williams and Herrup, 1988). In the following review, we will summarize evidence about the specific mechanisms of control of cell number for a variety of components of the visual system and evaluate the consequences of these mechanisms in the larger domain of visual system function and control of cell number in the brain overall.

1.1. CONCEPTUAL FRAMEWORKS IN WHICH THE CONTROL OF CELL NUMBER HAS BEEN INVESTIGATED

In answering the question of why organisms have come to be in their current state or, in this case, why the visual system of a certain animal contains a certain number of cells, a variety of types of explanations can be offered. First, an explanation could be given in terms of the function of the visual system and its optimal design: why a feature is necessary for proper visual functioning. For an example of this type of explanation, typically used by neuroanatomists, physiologists or psychophysicists, the number of cells in the lateral geniculate nucleus should equal the number of transmission cells in the retina so as to not to lose spatial resolution. Alternatively, an explanation could be given in terms of the evolutionary history of the animal. Comparative and evolutionary biologists might point to the size in the lateral geniculate in closely related species of comparable body size as the reason for the particular number of geniculate cells in the species of interest. Finally, the nature of the animal’s development might be given as the reason. Developmental neurobiologists might argue that because of competition for terminal space in the visual cortex, only a certain number of lateral geniculate cells might receive enough trophic substance to survive, thus determining their number.

These explanations represent different aspects of biological argument and are not contradictory, but are too often kept separate. In the following review, we will principally discuss information from developmental neurobiology on control of cell number in the visual system, and we will attempt to begin an integration of this information with comparative and evolutionary approaches. The contrast between these two fields is interesting, because for evolutionary biology the individual is a unit of variability, and the data to be explained are the variations in brain size and organization across individuals and species. For the developmental neurobiologist, a typical research approach is to determine what developmental processes conserve or stabilize the cell number of a particular brain area, or define a constant ratio relationship between cells in interconnecting populations in the nervous system: i.e. how, in individual animals, development is regulated against variability. Since species variations in brain organization must arise out of variations in developmental programs, these two approaches could profitably be integrated (Finlay et al., 1987; Wikler and Finlay, 1989). In particular, we will ask if there is any information from the developmental neurobiology of the visual system which might shed light on the patterns observed in visual system evolution.

1.2. COMPARATIVE APPROACHES TO THE CONTROL OF CELL NUMBER

The nature of developmental control of cell number for an entity like the “visual system” is poorly understood. The central issue is: what units of the visual system or brain independently vary from species to species? At what level of organization in the nervous system can cell number vary independently, so that a change might be selected for? There are a variety of approaches to this question that come from comparative anatomy, all of which account for part of the variations between species. Some emphasize overall brain–body or metabolic relationships, some particular organ systems (like the cortex or cerebellum) and some functional systems (like the visual system).

Students of allometric relationships of brain and
body point to the lawful relationships of brain and body size (for a comprehensive review see Eisenberg, 1981). Within any vertebrate radiation, overall brain size is an exponential function of body size. Both of these variables in turn can be related to length of gestation, to rate of growth and to other metabolic constraints in early development. The relative constancy of this function across vertebrate radiations has suggested that if an animal is selected for a certain body size or rate of development, a certain brain size is concurrently specified by whole-animal genetic constraints. It is also possible, however, that these allometric regularities represent stable, multifactorial solutions to selection pressures encountered repeatedly and not direct genetic control of both body size and brain cell number as a single specifiable unit (Mann et al., 1988).

At any particular body size, however, there is a large residual variation in brain size unaccounted for by allometric regularity, as much as 5–10 to 1 in mammals (Northcutt, 1981). To account for this residual variability, a second description of the nature of change in the vertebrate brain is “encephalization” (Jerison, 1973); that complex system shows increases in the relative importance of the telencephalon, particularly neocortex (or the cerebellum, Northcutt, 1981). The underlying hypothesis of encephalization is that particular structures like the neocortex are particularly likely to show an increase in size over evolution, within a functionally defined system like the visual system, and perhaps across several functionally-defined systems.

Residual variation in brains could also be accounted for in part by hypertrophy or atrophy of particular functional systems. For example, animals are often described as “more visual” or “less visual” based upon the extent to which they depend upon vision in their behavior, and their corresponding anatomy is often thought to show this distinction throughout, from size of eye to corresponding visual cortex to visuomotor components, as in the traditional textbook comparisons of rat and monkey. However, it is not known whether “the visual system” is a genetic unit all of whose parts might become smaller or larger in concert: a systematic study of the relative size and number of components in animals classified as more or less visual has not yet been done. Visual system components might only change in a piecemeal fashion.

To resolve and integrate these approaches, information on the numerical relationships of numbers of cells in different visual system structures in a variety of species is necessary. However, this information is quite sparse, and developmental investigations sparser still. We will first list what is known about the numerical relationships of visual system structures in a few widely studied mammals for a preliminary sense of what, if anything, is conserved across the visual system in the numerical relationship of components. Next, we will review developmental investigations of control of cell number to determine what regulatory forces exist, and how they might account for phylogenetic trends in visual system organization.

### 1.3. NUMERICAL RELATIONSHIPS OF VISUAL SYSTEM COMPONENTS IN MAMMALS

Very few mammals have been assessed comprehensively for the number of neurons in their retinæ and associated central structures. Since existing studies are not systematic and overrepresent rodents, definitive conclusions about phylogenetic trends, or regularities in ratio relationships between visual system structures are difficult. Nevertheless, inspection of these data can produce some useful initial observations (Table 1).

For closely related animals that differ in body size, how does the visual system differ? The most systematic data available come from a recent study of Hallet (1987), who studied scaling relationships in the visual system for the mouse and rat, animals which have similar overall morphology and visual ecology, but different body size. He concludes that the two species have linearly scaled optics (i.e. cross sections of their eyes are superimposable with an appropriate scaling

<table>
<thead>
<tr>
<th>Animal</th>
<th>Photoreceptors</th>
<th>RGC</th>
<th>LGN</th>
<th>SC</th>
<th>VC (17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamster</td>
<td>—</td>
<td>72</td>
<td>36</td>
<td>100</td>
<td>760</td>
</tr>
<tr>
<td>Gerbil</td>
<td>—</td>
<td>160</td>
<td>140</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mouse</td>
<td>6,412</td>
<td>50</td>
<td>21</td>
<td>90</td>
<td>440</td>
</tr>
<tr>
<td>Rat</td>
<td>23,570</td>
<td>110</td>
<td>120</td>
<td>394</td>
<td>1,100</td>
</tr>
<tr>
<td>Cat</td>
<td>150</td>
<td>—</td>
<td>—</td>
<td>29,000</td>
<td>—</td>
</tr>
<tr>
<td>Monkey</td>
<td>127,000</td>
<td>1,300</td>
<td>1,400</td>
<td>—</td>
<td>150,000</td>
</tr>
<tr>
<td>Human</td>
<td>—</td>
<td>1,100</td>
<td>—</td>
<td>—</td>
<td>538,000</td>
</tr>
</tbody>
</table>

Entry = cells x 1000.

Legend: RGC, retinal ganglion cell; LGN, lateral geniculate nucleus; SC, superior colliculus; VC, visual cortex.

1. Mesocricetus auratus: RGC, from Linden and Esberard, 1987; LGN, Finlay et al., 1985; SC and VC, unpublished results, this laboratory.
2. Meriones unguiculatus: RGC, unpublished results, this laboratory.
3. All mouse (C57Bl/6J pigmented) and rat (Long-Evans) as reviewed in Hallet, 1987; also Peters, 1987 for VC.
factor), and equal photoreceptor spacings. Since the retinal area is four times larger in a rat than a mouse, the rat has thus four times as many photoreceptors. Note, however, that while photoreceptors and central structures change their numbers by a factor of four between these animals, number of ganglion cells changes only by a factor of two (Table 1), and central structures change variable amounts between two and four.

For closely related animals of the same body size but different visual capacity, how does the visual system differ? Gerbils (Meriones unguiculatus) and hamsters (Mesocricetus auratus) present such a comparison. First, visual system size is obviously dissociable from body size: the gerbil has more than twice the retinal ganglion cells of the hamster, and 3.5 times more cells in the lateral geniculate body. Interestingly, the scaling relationships are quite comparable to that seen in the mouse/rat comparison. This suggests that the visual system can in fact change as a unit, but does so without preserving 1:1 ratios of cells in its components as the visual system becomes larger or smaller.

For the more distantly related species shown here, the number of ganglion cells is peculiarly unrepresentative of either intuitions about the animal’s visual capacity or known information on their visual acuity (Wilkinson, 1984); the topographic arrangement of these cells is quite different, however, and does correspond to behavioral acuity (Hughes, 1977).

For any one species the numbers of cells in these various brain areas do roughly covary, as might be expected from gross allometric studies of the relationship of brain to body size (Eisenberg, 1981). However, there is little to suggest a constant ratio relationship between the numbers of cells in these visual nuclei. The ratio of ganglion cells to number of cells in subcortical target nuclei does vary less than ratios involving the cortex. Particularly striking is the variability of absolute numbers of neurons in primary visual cortex, and the varying ratios of the number of cells in primary visual cortex and the lateral geniculate nucleus, which in this data set ranges from 2.5:1 (rat) to about 100:1 (human). Humans have only 10 times the number of ganglion cells as do rats, but 400 times the number of cells in primary visual cortex (Hallet, 1987; as reviewed in Peters, 1987). In addition, extreme individual variability in the area of striate cortex in macaques has been described (Van Essen et al., 1984); in a study of 31 monkeys, the area of striate cortex ranged from 690 mm² to 1560 mm².

Failure to find a constant ratio relationship between these areas is not surprising in that each of these nuclei connect to other brain areas, and the neurons that compose them vary in a number of ways, including somal conformation and size, and axonal branching patterns. Attempts to assemble information like that contained in Table 1 are instructive, however, in demonstrating how little is actually known about fundamental regularities in system organization across animals, or what sources of developmental variability produce the eventual differences in neuron number seen here. Of particular interest for this review is whether experimentally-induced differences in convergence ratios between visual nuclei in any single animal can account for cross-species variability, particularly the extreme variation in visual cortex.

### 1.4. Variability in Convergence Ratios of Cells within the Visual System

The convergence ratio between cells in the visual system has been the subject of much study. Differential convergence between rods and cones and onto the bipolar cells in the retina, variable convergence of cones onto bipolar cells from the center to the periphery of the retina, and the nature of convergence from thalamus to cortex have been studied particularly well in cats and monkeys (Sanderson, 1971; Mellwain, 1975; Wilson and Sherman, 1976; Peichl and Wassle, 1979; Connolly and Van Essen, 1984; Schein and de Monasterio, 1987).

Central to this discussion is the fact that functional “streams” (Van Essen, 1979; Van Essen and Maunsell, 1983) in the visual system preferentially magnify different areas of the visual field, as expressed as cells per visual angle. This is most notably true for rods and cones, but is also true for the major cell classes of the ganglion cell layer. X cells (cats) or P cells (monkey) preferentially represent central retina, while Y, W (cat) and M cells have flatter distributions (Wilson and Sherman, 1976; Schein and de Monasterio, 1987). Yet, these “streams” must be accommodated in the same coordinate system of visual space laid out in primary visual cortex, and in fact must often be represented by the same cells. This requires that convergence ratios between pre- and postsynaptic cells be systematically altered for particular cell classes across the visual field. An example of this is the convergence of magnocellular (M) and parvocellular (P) geniculate laminae onto striate cortex in the macaque (Schein and de Monasterio, 1987). They argue that across the visual cortex, the ratio of presynaptic P cells to striate cortical cells remains constant. However, the proportional number of M cells is higher in the periphery, so the convergence ratio increases for M cells from center to periphery by about a factor of 7. How does the structural basis for this difference in convergence ratios (for example, by change in axonal arbor size or alteration in the number of presynaptic cells contacting postsynaptic cells) come about during development?

This representational problem occurs numerous times within the visual system; For example, area 17 preferentially represents the center of the visual field, the superior colliculus comparatively represents the periphery, and area 17 projects to the superior colliculus, in spatial register. This problem is almost certainly not unique to the visual system, and the constraints on the mechanisms by which arrays of variable cell number are mapped onto each other would be of extreme interest.

In the following sections we will review the literature, with particular emphasis on our own studies, on experimental manipulations of the developing visual system. Of interest will be how adult cell numbers are produced through processes of cell generation and death, and whether ratios of cell numbers are regulated. The mapping problem of variable convergence ratios, and the issue of what features of interconnecting populations are stabilized during develop-
opment are the fundamental questions which guide this study.

2. DEVELOPMENTAL STUDIES OF CONTROL OF CELL NUMBER

2.1. THE RETINA: RETINAL GANGLION CELLS

2.1.1. Normal cell addition and loss

Retinal ganglion cells are the first cells produced in the developing mammalian retina (Sidman, 1961; reviewed in Polley et al., 1989). Several species show a central to peripheral wave of retinal ganglion cell production, while others show a flat distribution (Sengelaub et al., 1986; Wikler et al., submitted). The presence or absence of spatial gradients in initial cell production is related to the eventual cell distribution of the retina: whether its growth will be uniform, to produce a uniform cell distribution, or non-uniform, producing the growth pattern characteristic of an area centralis or visual streak (Wikler and Finlay, 1989). As retinal ganglion cells leave the mitotic cycle, differentiate and begin to establish central connections, cells in the ganglion cell layer begin to degenerate and die (Sengelaub and Finlay, 1982; Sengelaub et al., 1986). Since the ganglion cell layer consists of two neuronal populations, ganglion cells and displaced amacrine cells, much effort has been expended to determine the identity of the cells lost. These include morphological and ultrastructural investigation (Young, 1984; Cunningham et al., 1982; Wong and Hughes, 1987a,b; Provis, 1987; Penfold and Provis, 1986); labelling retinal ganglion cells retrogradely with HRP, and counting the changes in labelled cell number (Perry et al., 1983; Henderson et al., 1988); labelling of degenerating debris by its birthday with tritiated thymidine (Sengelaub et al., 1986); and comparison of changes in numbers of axons in the optic nerve with changes in cell number and distribution in the ganglion cell layer (Braekevelt et al., 1986; Provis et al., 1985a,b; Chalupa and Williams, 1984; Williams et al., 1986). Taken together, these studies conclusively show a major loss of ganglion cells, between 50 and 90% in every mammalian species studied (quokka, Braekevelt et al., 1986; albino rat, Crespo et al., 1985; rat, Dreher et al., 1983; Henderson et al., 1988; Jeffrey and Perry, 1982; cat, Ng and Stone, 1982; monkey, Rakic, 1983; hamster, Sengelaub and Finlay, 1982; Sengelaub et al., 1986; cat, Shatz and Sreetavan, 1986; gerbil, Wikler et al., submitted; rabbit, Robinson et al., 1986). There is some indication that different sub-classes of ganglion cells may die in different proportions: the earliest generated, large ganglion cells in the hamster and gerbil retinae show the greatest proportional loss (Sengelaub et al., 1986; Wikler et al., submitted); in the cat, cells of different types show different patterns of death associated with their projection laterality (Leventhal et al., 1988).

Enough species have been studied so that it is reasonable to look for phylogenetic trends, or functional variations in visual systems associated with greater or lesser amounts of death. There are intrinsic problems associated with these studies, however, which make any conclusions tentative. The principal method by which total cell loss has been ascertained is to compare the peak of axon numbers with mature axon numbers in the optic nerve. Since axon addition and loss are coincident in the optic nerve, and since the rate of addition and loss must vary between species, this method almost certainly yields inaccurate comparisons. In addition, in some species, the presence of substantial axon branching confounds this estimate (Braekevelt et al., 1986; but see Lia et al., 1985). Nevertheless, taking these estimates uncritically, the largest demonstrated axon losses are 80% in the cat (Williams et al., 1983, 1986; review in Shatz and Sreetavan, 1986) and the quokka, a rabbit-sized marsupial (Braekevelt et al., 1986). The other species cited previously show a range between 50 and 70%. No obvious relationships between the amount of cell death and any feature of visual system organization, such as visual system complexity or degree of binocular overlap, are obvious.

2.1.2. Generational control of retinal ganglion cell number

There is no evidence that retinal ganglion in mammals may be induced to proliferate early in development by reduction of their numbers, as has been demonstrated for amacrine cells in amphibians (Reh, 1987), or that the hormonal milieu influences the number or type of cells generated, as has also been shown in amphibians (Hoskins, 1989). Neither, however, have there been systematic tests of these possibilities. A hypothesis that a retinal ganglion cell with a centrally projecting axon might retract that axon and become an amacrine cell (Hinds and Hinds, 1983), has been largely discounted (Perry, 1981; Perry et al., 1983). Therefore, the number of ganglion cells originally generated is viewed to be unmodifiable, and developmental cell death has been the sole factor investigated for potential alterations in adult retinal ganglion cell number.

Several studies in non-mammalian vertebrates now indicate that the ventricular cells of the retina are pluripotent, giving rise to retinal neurons of all types (Wetts and Fraser, 1988; Holt et al., 1988). How the relative proportion of each cell type is fixed in the mammalian retina is unknown. The reciprocal relationship of the densities of some cell types in some retinas, for example, retinal ganglion cells and displaced amacrine cells of the ferret retina (Henderson et al., 1988), raises the interesting possibility that an increased density of a particular cell class might be "bought" at the expense of fewer divisions producing an alternate cell class for cell groups that are clonally related.

2.1.3. Efferent and afferent control of cell number

The three functional roles for cell death that have been systematically considered are numerical matching of retinal ganglion cells with their target and afferent availability, correction of errors of early connectivity, and sculpting of topographical inhomogeneities.
2.1.3.1. Target control of cell number

Retinal ganglion cells require efferent targets for their survival at all but the earliest stages of their development. Section of the optic nerve in any mammal studied results in the eventual death of all ganglion cells (see Allcutt et al., 1984). In tissue culture, retinal ganglion cell survival is improved by conditioning of the medium with appropriate target culture, retinal ganglion cell survival is improved by ganglion cells (see Allcutt state of the cells (Raju and Bennet, 1986).

Trophic requirements change with the maturational state critical for cultured cell survival, indicating that their survival at all but the earliest stages of their availability (Hamburger and Levi-Montalcini, 1949; Hollyday and Hamburger, 1976). Initial enthusiasm over this positive result for a time masked the further observation that the details of the behavior of spinal cord motoneurons and retinal ganglion cells are quite different: in normal development (Sperry, 1987) and in several experimental manipulations (Hamburger and Levi-Montalcini, 1949; Hollyday and Hamburger, 1976), spinal motoneuron number is related quite linearly to target availability (but see Lamb, 1980). Retinal ganglion cell number is related much more loosely to target availability. We will argue that branching of optic axons and considerable malleability in their terminal arbor size can account for this observation.

Increased target: early enucleation of one eye. Removal of one eye in development in the hamster provides greater terminal area and presumably lesser competition for terminal area for the remaining eye. This manipulation reduces the incidence of degenerating cells in the remaining eye (Sengelaub and Finlay, 1981), and at maturity there are greater numbers of cells of ganglion cell morphology in that eye (16%; Sengelaub et al., 1983). These “rescued” cells derive principally from the temporal retina in which, in the hamster as in other rodents, both the ipsilateral and contralateral projections arise. In addition, a component of this increased projection comes from ipsilaterally projecting cells of the nasal retina, an early aberrant projection which is stabilized by the early eye removal, to be discussed in more detail below (Insauri et al., 1984). This rescue effect has now been demonstrated numerous times by optic nerve counts after prenatal eye removals in monkeys (35% sparing; Rakic and Riley, 1983) and in cats (20% sparing; Williams et al., 1984; Chalupa et al., 1984; however, another less extensive study reports no sparing, Shatz and Sretavan, 1986). Rats also show similar stabilized projections, though a change in axon number has not been observed probably due to its small absolute magnitude (Crespo et al., 1985).

The substantial species differences in the percentage of cells rescued do not yet have a complete explanation. The relative number of spared cells is larger in monkeys, which has been attributed plausibly to their greater potential for binocular competition due to their greater binocular overlap (Rakic, 1986). However, the number of cells saved in the cat is considerably less, if all studies are taken together, despite the fact that the cat has binocular overlap not much less than the monkey. In the quokka, which also has large binocular overlap, no difference in cell survival in the remaining eye after early monocular enucleation is seen (Coleman and Bezalez, 1986). Note also, as in every case of sparing of cells after provision of greater terminal area, cell death is reduced but not eliminated, even in the case of the cat and monkey where available target area is nearly doubled for the remaining eye by the early enucleation.

Decreased target: striate cortex and lateral geniculate ablation. If lesser target is available for ganglion cells, cell loss is only sometimes increased, depending upon the particular postsynaptic structure damaged and the maturational state of the animal at the time of the damage. In rodents, removal of the visual cortex, which results in the complete transneuronal loss of the lateral geniculate nucleus, has no effect on retinal ganglion cell survival, as measured from numbers of cells in the ganglion cell layer (Perry and Cowey, 1979a,b; 1981; Linden et al., 1983; Raabe et al., 1986). The lateral geniculate nucleus in rodents accounts for about 15–20% of the total terminal volume of the combined tectum and geniculate, as measured in numbers of cells (Table 1), and most if not all cells projecting to the lateral geniculate nucleus in rodents also send a branch to the superior colliculus. Whether the small absolute volume of the cell loss or the presence of axonal branching, or both is the factor responsible for the lack of response to geniculate ablation is not known. In monkeys and cats, removal of primary visual cortex results in the selective loss of X cells, thought to occur since this class of cells projects exclusively to the lateral geniculate (minor projections to midbrain structures have been demonstrated but are apparently inadequate to sustain retinal ganglion cells), whereas Y cells branch to innervate the superior colliculus (Tong et al., 1982; Payne et al., 1984; Weller and Kaas, 1984).

Decreased target: superior colliculus ablations. Damage to the superior colliculus, the major target of the retinal ganglion cells in rodents, has variable effects which can principally be accounted for by the animal’s maturational state at the time of damage. In the hamster, removal of an average of 70% of the superior colliculus at birth, prior to the ingrowth of most optic fibers, results in only an 8% increase in cell loss (Wikler et al., 1986). In rats, if the damage occurs at birth, about 30% of the normal ganglion cell population is lost. If the tectum is destroyed at 5 days postnatal, 60% of the population is lost (Perry and Cowey, 1979a,b, 1981). Similar studies in the rat using kainic acid injections into the superior colliculus which have the advantage of not directly damaging axons, confirm this approximate magnitude (Carpenter et al., 1986). Since the hamster is substantially less mature than the rat at birth, the hamster results are a plausible extrapolation of the rat results. In both the hamster and rat, a progressive lack of reorganization of retinal arbors after early tectal lesions has been demonstrated to occur during this time period (So and Schneider, 1978; Perry and Cowey, 1982) which could account for the difference in retinal cell loss at different ages.
Partial losses of a target can be met without major cell loss, if there is enough time for retinal ganglion cell axons to establish a new terminal arbor of reduced size in the decreased target area. Ganglion cell survival thus reflects aspects of target availability, but there is little evidence for linear matching of ganglion cell number to target availability through developmental cell death.

2.1.3.2. Afferent control of cell number

Developing neurons may also require interactions with their afferents in order to survive; such trophic interaction has been demonstrated for the spinal cord (Okado and Oppenheim, 1984). The afference to retinal ganglion cells, the various amacrine and bipolar cells of the ganglion cell layer and the inner nuclear layer, has been the subject of fewer studies than the target control of cell survival, principally due to the difficulties of selectively manipulating the amacrine/bipolar population. In order to explore the role of afference, experimental studies have principally made use of the fact that enucleation, optic tract section and target ablation have different consequences for the ratios of afferents to target retinal ganglion cells than they do for the ratio of retinal ganglion cells to their targets.

Evidence that afferent input may in part regulate cell survival comes from the observation of the effects of early unilateral superior colliculus ablation in rats (Linden and Perry, 1982; Perry and Linden, 1982). Unilateral tectal lesions cause a loss of ganglion cells in the contralateral retina, as described previously (Perry and Cowey, 1979a,b). However, this loss is confined to the contralaterally projecting cells of the retina contralateral to the lesion: the numbers of ipsilaterally-projecting cells in this retina go up in number. The authors argue that these ipsilaterally-projecting cells, whose targets have not changed, are in a privileged position for access to afference, due to the loss of contralaterally projecting cells in the same area of retina. Their finding that retinal ganglion cell dendrites extended toward depleted areas lent support to this argument. While other explanations involving rerouting or selective loss of cell types might also account for these results, as these authors note, the likelihood that afference does modulate early cell survival is high, and developmental depletions of particular amacrine and bipolar cell populations with selective toxins will eventually disambiguate these results. Dendritic competition and competition for targets may interact to determine the final distribution of cells across the retina (Linden and Serfaty, 1985).

2.1.4. Error correction

Errors, defined as projections observed in neonates not observed in adults, occur in the early choices of laterality, target nucleus and topography for retinal ganglion cells. It has been conclusively demonstrated that it is cell death that removes early errors of projection laterality (Sengelaub and Finlay, 1981; Jeffrey and Perry, 1982; Insausti et al., 1984; Cowan et al., 1984). Errors of choice of target nucleus are also observed in early development, but it is unknown if cell death removes them (Frost, 1984).
It has been established that aberrant ipsilateral projections establish synapses (Jeffrey et al., 1984) and that normal neuronal activity is required for their removal (Fawcett et al., 1984). Blockade of normal activity also alters the pattern of retinal ganglion cell survival in vitro (Lipton, 1986). Thus, the mechanism of ejection of aberrant ipsilateral projections is likely to be activity-dependent sorting, which results in the death of the projecting neuron. Why this type of target loss results in the death of neurons, while major target ablations often do not result in neuronal death will be discussed in conclusion.

The absolute magnitude of errors of projection laterality is small, with estimates ranging from 1-4% (Jeffrey and Perry, 1982; Sefton and Lam, 1985). While the number of errors of target choice has not been determined, qualitative estimates would also make this number quite small (Frost, 1984). Thus, the removal of gross lateral and targeting errors can only account for a very small fraction of naturally-occurring cell loss. A somewhat larger magnitude of error correction has been described in the developing retinotectal system at the level of order in topographic projections (O’Leary et al., 1986; Catsicas et al., 1987). A role of cell death in the local ordering of projections may contain the key to the reason for the large magnitude of cell death in various developing vertebrate systems (Section 4.1).

2.1.5. Sculpting

During the period of retinal development when cell death occurs, the retinal ganglion cell layer begins to change from a sheet of cells of roughly uniform density, to a surface showing the local specialization of areas of high cell density such as an area centralis or visual streak (some of this specialization also occurs after the period of cell death, through differential retinal growth; reviewed in Wikler and Finlay, 1989). Early excess cell death in the periphery might thus initiate or at minimum contribute to the production of local specializations (Sengelaub and Finlay, 1982). Proportionately greater cell loss in the retinal periphery has been demonstrated in the hamster and quokka (a marsupial), using the method of comparing distributions of tritiated-thymidine labeled cells before and after the period of cell death (Sengelaub et al., 1986; Beazley et al., 1989). In the human retina, a very much greater incidence of degenerating cells in the retinal periphery suggests the same effect (Provis, 1987). In other species, the presence of differential cell loss is controversial (cat, Lia et al., 1987; Stone and Rappaport, 1986 vs Wong and Hughes, 1987a,b;c; Shatz and Sretavan, 1986), or ambiguous (ferret, Henderson et al., 1988; gerbil, Wikler et al., submitted) or demonstrated to be a minor effect (rat, Perry et al., 1983; rabbit, Robinson et al., 1986). The variability across species is not accounted for by the type of retinal specialization possessed by the animal, nor by the degree of center/periphery density disparity. No sensible phylogenetic analysis can be made with the small number of species sampled.

We suggest that the marked topographical inhomogeneities seen in cell loss in the early development of the retina may well reflect a solution to the convergence problem arising from mapping cell groups with different spatial distributions onto single terminal area, such as the distribution of X and Y cells discussed previously (Section 1.4). If the competition for retinotopically-defined terminal sites varies across the visual field for different cell classes, the probability of death would be higher for certain cell classes in particular retinal locations. As a hypothetical example, if W cells are comparatively more numerous in the visual periphery than Y cells but must share retinotopically defined terminal sites in the superior colliculus, the W cells would be at a disadvantage claiming terminal sites in the periphery of the visual field compared to their success in the center, and peripheral W cells might show a higher incidence of death. The fact that different cell classes do show different absolute amounts of cell death (Sengelaub et al., 1986) is consistent with this hypothesis.

2.2. The Retina: Amacrine Cells, Bipolar Cells, Horizontal Cells and Photoreceptors

2.2.1. Normal cell addition and loss

The neural retina is generated in several overlapping gradients: the first, retinal ganglion cells, amacrine cells and cones, and second, bipolar cells and rods (see review by Polley et al., 1989). For mammals, there is no evidence as yet that the amount of generation of any of these cell classes may be influenced by the number of pre-existing cells of the same class as has been shown in the amphibian (Reh, 1989). Transection of the optic nerve in the rat results in no changes in the ongoing rate or pattern of mitosis in the ventricular zone (Beazley et al., 1987).

Following the termination of generation of each retinal cell class, a period of cell death occurs (mouse: Young, 1984; rat: Kuwabara and Weidman, 1974; Spira et al., 1984; Cunningham et al., 1982; cat: Wong and Hughes, 1987c; Horsburgh and Sefton, 1987; Robinson, 1988; human: Penfold and Provis, 1986). Cell death in all of these cell classes has been inferred from the presence of pyknotic cells in the appropriate location, with ultrastructural confirmation in most cases. For amacrine cells, the absolute number of cells has been shown to decline (Perry et al., 1983; Wong and Hughes, 1987a,b; Henderson et al., 1988). Other cell classes have not yet been investigated for alterations in absolute neuron number.

2.2.2. Efferent and afferent control of cell number

2.2.2.1. Photoreceptors

A specialized type of cell loss has been hypothesized for the photoreceptor cells. Photoreceptor cells located ectopically in the inner nuclear layer in early development show a pronounced and specific degeneration (Spira et al., 1984; Robinson, 1988) which has been interpreted as a consequence of a migrational disorder resulting in failure to make connectivity appropriate to that cell class. However, a direct
demonstration that photoreceptors must make synaptic contact to survive has not been made.

2.2.2.2. Amacrine cells and bipolars

Both the displaced amacrine cells of the ganglion cell layer and the amacrine cells of the inner nuclear layer normally show a substantial amount of cell loss (Perry et al., 1983; Sengelaub et al., 1986; Wikler et al., submitted; Henderson et al., 1988; Horsburgh and Sefton, 1987). The cause of this loss is unknown, in that this cell class has been repeatedly shown to be resistant to complete removal of its principal target, the ganglion cell population, during development or at adulthood (Miller and Oberdorfer, 1981; Perry, 1981). Neither total cell number, nor the location and number of pyknotic cells, nor the incidence of particular amacrine cell subclasses known to be directly presynaptic to ganglion cells has been shown to change after optic nerve section (Osborne and Perry, 1985; Beazley et al., 1987; Horsburgh and Sefton, 1987). Similar independence has been indicated for bipolar cells (Beazley et al., 1987). In transplant studies where ganglion cells fail to make connections with their host tissues and die, amacrine and bipolar cells survive (McLoon and Lund, 1984). Manipulation of afference to these cells has not yet been done, and the relationship of amacrine and bipolar survival to afferent innervation would be very useful information.

The reason for the independence of retinal interneuron number from their targets is unclear, and the cause of the substantial cell death in this cell class is a further mystery. In few other structures has a contrast between interneurons and projection neurons been investigated. In the cerebellum, however, interneurons show a higher rate of cell loss than projection neurons (Caddy and Biscoe, 1979). Several useful avenues for investigation suggest themselves. Since many or most interneurons do not have the problem of distant target acquisition or topographic mapping to solve, the nature of their trophic requirements might be quite different: residual intrinsic connectivity with other interneurons might be enough to sustain cells in early development. Whether death in these cell classes is related to normal synaptic activity is unknown. The often non-spiking nature of much interneuronal transmission may require a different mechanism for activity-dependent sorting, if it in fact occurs.

2.3. Superior Colliculus

2.3.1. Normal cell addition and loss; sculpting

Neurons that compose the retinorecipient zones in the superior colliculus are generated over approximately the same period of time that retinal ganglion cells are generated. The first autoradiographic demonstration that histogenesis in the mammalian brain is largely unaffected by its afferent input was made for the superior colliculus by DeLong and Sidman (1962): early enucleation partially deafferenting the superior colliculus did not change the rate of cell generation in the colliculus. Pyknotic cells in early collicular development have been described several times (Arees and Astrom, 1977; Giordano and Cunningham, 1978; Finlay et al., 1982; Cunningham et al., 1982), and the amounts of cell loss observed in hamsters probably correspond to about 20% of the originally generated cell cohort of the superficial cell layers, and about 40% of the lower layers (Finlay et al., 1982). The pattern of cell death corresponds to the maturational gradient of retinal innervation of the superficial layers of the superior colliculus (Cunningham et al., 1982).

The incidence of pyknotic cells is much higher in the retinotopically defined periphery of the superficial gray layer of the superior colliculus, over all developmental stages (Finlay et al., 1982). In the intermediate and deep gray layers, the incidence of pyknotic cells is higher centrally. This spatially inhomogeneous distribution of cell loss may relate to the developmental problem of mapping together representations of the visual field that differentially magnify or represent different parts, as discussed previously. However, this hypothesis has not been directly demonstrated, and there is partial evidence against the hypothesis that retinotopic gradients in the density of afferents produce this effect: the gradient persists at an elevated level of cell loss if the superior colliculus is denervated by early enucleation (Walker et al., 1986). The retina therefore does not impose its spatial inhomogeneity in cell loss directly upon its target.

2.3.2. Efferent and afferent control of cell number

No study of cell survival in the colliculus after manipulation of its targets has been made. Instead, interest has centered on afferent control of cell number, principally because of the relative ease of deleting inputs to the superior colliculus. Denervation of the superior colliculus by early monocular or binocular enucleation increases early cell death and decreases adult cell number (DeLong and Sidman, 1961; Finlay et al., 1986). The only changes observed in early cell death, however, occur in regions that are nearly totally denervated of their retinal input: after monocular enucleation, elevated cell loss is seen only in the monocular section of the colliculus contralateral to the enucleation (Fig. 2). The partial denervation occurring in binocular zones has no effect. (This is also seen in the lateral geniculate body, to be discussed in Section 2.4.2.)

One report linked a possible increase in innervation (produced by an early visual cortex lesion, which causes degeneration of the lateral geniculate body and potential rerouting of afference from the lateral geniculate to the superior colliculus) to a decrease in cell loss in the superior colliculus (Cunningham et al., 1979). Our attempts to replicate this phenomenon failed, however (Raabe et al., 1986). Another attempt to produce collicular hyperinnervation through partial tectal lesions also produced no change in the amount of collicular cell loss (Wikler et al., 1986). We interpret these results in the following manner: afferents are normally in excess and compete for terminal space. Thus, only major denervations of afferent input are detectable by this target tissue, and increases in afferent availability are also ineffective, since afferents are normally in excess.
In both the hamster and monkey, the cell loss within the lateral geniculate nucleus is strikingly inhomogeneous, with the greatest concentration of degenerating cells seen in the ventral margins of the nucleus, corresponding to the retinotopic periphery. Whether this represents a solution to the mapping problem for projections with intrinsically different magnification described previously, or the deletion of a particular cell class is as yet unknown (Sengelaub and Finlay, 1985; Williams and Rakic, 1988).

2.4.2. Afferent and efferent control of cell number

The lateral geniculate nucleus critically depends upon the integrity of its efferent target, the visual cortex, for its survival. Damage to the visual cortex early in development results in nearly complete loss of the lateral geniculate body, particularly in rodents where the projection from the lateral geniculate body to striate cortex is exclusive (Perry and Cowey, 1979a,b; Cunningham et al., 1979; Raabe et al., 1986; Pearson et al., 1981). The lack of multiple targets for the lateral geniculate nucleus, combined with absence of reorganization or redirection of the geniculo-cortical pathway after cortical damage (Miller et al., 1987) may account for this exceptionally high sensitivity to target availability. Recently, a diffusible protein associated with the visual cortex has been shown to prolong the survival of lateral geniculate neurones after cortical ablation (Cunningham et al., 1987).

After deafferentation by monocular or binocular enucleation, the lateral geniculate body shows a pattern of induced cell loss much like that already described for the superficial layers of the superior colliculus. Unlike target removal, cell loss produced by deafferentation is not total: values ranging from 30-50% cell loss have been reported (Finlay et al., 1986; Heumann and Rabinowicz, 1980; Rakic and Williams, 1986). Partial deafferentations in areas of binocular overlap produce little or no increase in cell death. The interpretation of these results we offer is as above (Section 2.3.2): afferents are normally in excess, and only substantial removals are detectable by target tissues.

2.5. Parabigeminal Nuclei: Efferent and Afferent Control of Cell Number

The parabigeminal nucleus, a midbrain site of reciprocal connectivity between the contralateral and ipsilateral superior colliculus, offers an interesting opportunity to both dissociate the effects of afferent and efferent connectivity and also to examine their interaction because it has divisions that are purely afferent to the superior colliculus, purely efferent, or both (Linden and Perry, 1983; Linden and Pinon, 1987). Moreover, the nucleus has very few connections with structures other than the superior colliculus, and thus the deafferentation and target removal produced is effectively total. Consequent to unilateral colliculus lesions, both areas efferent and afferent to the colliculus show increased cell death (though not total cell loss). The time course of target- and afferent-induced death is different, however, with

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**Figure 2.** Qualitative summary of results from our laboratory on the effects of various developmental manipulations of afference on patterns of cell death and corresponding adult cell number. The direction and size of the arrows (of three sizes) indicate the direction and size of the manipulation and the induced change in cell number through changes in cell death. Large black arrow: complete ablation or major addition of excess target; complete reactive cell loss or savings. Medium gray arrow: partial target ablation; substantial, but not total cell loss or savings. Small gray arrow: small to negligible reactive cell loss. Whether axons branch with respect to the target of interest is also included. RGCl, retinal ganglion cell layer; LGNd, dorsal lateral geniculate body; LGNv, ventral lateral geniculate body; SC, superior colliculus; VS, visual cortex, area 17.

2.4. LATERAL GENICULATE NUCLEUS

2.4.1. Normal cell addition and loss: sculpting

As in all other visual structures, neurons are overproduced and eliminated in the early development of the lateral geniculate nucleus. This cell loss occurs early in the establishment of the efferent and afferent connectivity of the lateral geniculate, during the period of establishment of retinotopic maps, but well before the segregation of ocular dominance columns (Williams and Rakic, 1988). The presence and spatial distribution of cell loss has also been described in several rodents (mouse: Heumann and Rabinowicz, 1980; rat: Matthews et al., 1982; Satorre et al., 1986; hamster: Sengelaub et al., 1985). Amounts of cell loss reported are in the 25–40% range for all species. In the monkey, the amount of cell loss is laterally asymmetric, with significantly less cell loss on the right side, raising the interesting possibility that thalamic cell death might produce or reflect some aspects of lateralization of the neocortex.
afferent-induced death protracted with respect to both normal cell death and target-induced death. Target and afferent effects interact so that no cells survive a combined target and afferent denervation.

2.6. Visual Cortex

2.6.1. Normal variability in adult neocortical cell number

Different species vary greatly in cortical area and in total number of cortical neurons (Table 1). In addition, there is significant variability between individuals within a species in the size of striate cortex (Van Essen et al., 1984), and presumably in the size of other cortical areas as well. It is unknown whether these individual differences arise from differences in cell generation or cell loss.

In contrast to the variability seen in total cortical cell number, there is some evidence for conservation of the number of neurons in a “unit column” of cortex. Studies by Rockel et al. (1980) have suggested a uniformity in neuron number per column across various areas of the lateral convexity of neocortex. (It should be noted here that in most cases discussed below, the investigators used criteria for counting that would include only neurons, and not glial cells.) These authors counted the number of cells in a 30 μm cortical column in several different cortical areas; motor (area 4), somatosensory (area S1), frontal (area 9), temporal (area 22), parietal (area 7) and striate (area 17) cortex in several different species (mouse, rat, cat, monkey and human). They found that despite the variation in cortical thickness between areas and species, the number of cells in a cortical column remained relatively constant (approximately 110 cells/column). In agreement with this finding, Beaulieu and Colonnier (1983, 1985) confirmed that in areas 18, PMLS, and the monocular portion of 17 in the cat, the number of cells per column varies by less than 10% between them. However, although there may be uniformity between some areas within a species, other authors do not agree that there is uniformity between species. In particular, data from several laboratories indicates that the cat has about half the number of neurons per cortical column as the macaque (see Peters, 1987, for review).

An exception to the uniformity among the areas Rockel et al. (1980) studied was in the binocular portion of area 17 in the macaque, which had 2.5 times the number of cells per column compared to the other areas (Rockel et al., 1980; see also O’Kusky and Colonnier, 1982; and the excellent review by Peters, 1987). In the cat, Beaulieu and Colonnier (1983, 1985) reported 30% more cells per column in the binocular area of 17 than in the monocular region of 17, area 18, or the posteromedial suprasylvian cortex. Cragg (1967), in an earlier comparative study, also found that the number of neurons per unit volume in the binocular portion of 17 in the macaque is much greater than that in the monocular portion of 17 in the cat or rat. The monocular region of the macaque area 17 was not counted. Peters (1987) has recently confirmed this observation. Thus, while it is not clear whether there is an overall uniformity in cell number between species, it is well established that the number of cells per column in the binocular portion of 17 is much expanded compared to other areas in both the monkey and the cat.

Investigators who have examined a wider array of cortical areas disagree with Rockel et al.’s idea of constancy in the number of cells in a cortical column as outlined above. The particular areas which Rockel et al. (1980) examined (all resided in the lateral convexity) do not reflect the full extent of variability in thickness seen between various neocortical areas. For example, Finlay and Slattery (1983) (see Section 2.6.3.4) investigated areas outside the lateral convexity in the hamster (29b, 29d, and 27) and found more variability in the number of cells per column between different areas than did Rockel et al., challenging the concept of strict uniformity. Area 17 had the highest number of columns per column, suggesting that there may be an upper limit; that thickness and cell number per cortical column can vary to some extent but never exceed a certain limit which is reached in the binocular part of 17. In addition, they found that in the medial cortex, values fall well below this value (cf. Bok, 1959). One might still postulate, however, a basic pattern on which cortical areas are constructed (within a species) that maintains the number of cells per cortical column in most portions of the lateral convexity, but with a potential for variation both above and below this value. This variation might depend on such factors as differential generation or death of neurons between different cortical areas.

2.6.2. Normal cell generation and death in the visual cortex

2.6.2.1. Generation and migration

Cortical neurons are generated from columnar epithelial cells residing in the ventricular zone (Boulder Committee, 1970; Sidman et al., 1959). After their birth (last cell division) neuronal cells migrate out to form the cortical plate, with each wave of cells coming to reside nearer the pial surface than the previous generation; thus the cortex is said to develop in an “inside out” sequence (Rakic, 1974; Angevine and Sidman, 1961, 1962; Luskin and Shatz, 1985; see McConnell, 1988, for review). Rakic suggested that the cells migrate along radial glial fibers, in part because the migrating neurons remain in very close apposition to the radial glia until they reach their destination (Rakic, 1971, 1972, 1974).

Rakic (1988) has recently proposed a “radial unit hypothesis of cortical parcellation” to explain how the generation of different cytoarchitectonic areas occurs. According to this hypothesis, prospective cytoarchitectonic areas arise from a number of proliferative units generated from progenitors at the ventricular layer. Each proliferative unit would generate a single “ontogenetic column”. If each proliferative unit is given approximately the same amount of gestational time to generate all of its daughter cells, and the rate of cell division and death does not differ between areas, the thickness of the cortex would remain relatively constant. In contrast, longer generation times would lead to thicker cortices. Indeed,
neurogenesis in Area 17 lasts twice as long as in cingulate cortex (Rakic, 1974, 1982), which may at least in part explain the increased thickness of area 17. Rakic (1988) proposes that changes (evolutionary or developmental) in the total size of a cyto-architectural area are accomplished by changing the number of proliferative units.

Thus, differences in generation of cortical cells between different cortical areas are one factor in the "sculpting" of the cortex. However, the differences in the pattern of lamination between areas are more striking than the differences in thickness, and cannot be explained by the radial unit hypothesis as presently interpreted. This issue will be discussed further in Section 2.6.3.4.

2.6.2.2. What is the normal pattern of cell death in visual cortex?

Cell death in the neocortex is a very significant event during the development of the neocortex. Absolute cell counts indicate cell losses in layers II–IV of up to 50% (Heumann and Leuba, 1983). This measure is confounded, however, by the simultaneous occurrence of migration and cell loss, and actual incidence of death is probably greater than 50%. Finlay and Slattery (1983) have examined cell death in five areas of hamster neocortex: Areas 17, 18b, 29b, 29d and 27. These areas were chosen because they show a great deal of variation in their final thickness and density. They found that not all cell death occurs in the last generated, upper layers (II–IV), and particularly in II–III. Very little degeneration was seen in layers V–VI. This was also noted by Heumann and Leuba (1983). Furthermore, the amount of degeneration seen during development in these upper layers predicted the eventual cortical cell number in each of the five areas.

The above results suggest that differential patterns of cell death are another factor which serve to "sculpt" the cortex and thus give rise in part to the differences in cortical cell number between various cortical areas. This is done primarily by variation in the extent of neuron death in the upper layers I–III. However, there is still a substantial amount of death seen even in area 17 (approximately 30%), which is the area that has the greatest final number of neurons per column, suggesting that cell death may serve some function in addition to sculpting.

Luskin and Shatz (1985) have described a population of cells termed the subplate cells, which were generated quite early in development. They reside just underneath the cortical plate at the time when thalamocortical afferents have sent their processes into the subplate area. The thalamic afferents remain in the subplate area while their potential targets, the layer IV cortical cells, migrate past them. After migration is complete and the thalamic afferents have contacted their target cells, the subplate cells die. Luskin and Shatz suggested that the subplate cells serve as temporary targets for the thalamic cells to sustain them until the cortical targets are in place. This phenomenon is reminiscent of the programmed cell death observed in invertebrates (Horvitz et al., 1982), where certain cells or populations of unidentified cells survive only transiently. Some of the cortical cell death that serves in the sculpting process may be "programmed" in a similar sense.

2.6.3. Efferent and afferent control of cell number

2.6.3.1. Error correction

In non-cortical systems, cell death has been demonstrated to operate in correction of early errors of projection (Lamb, 1976, 1977; Bennett and Lavidis, 1981; Cowan et al., 1984; O’Leary et al., 1986; Catsicas et al., 1987; see review in Section 2.1.4). However, the removal of cortico–cortical and cortico–subcortical connections is brought about by collateral elimination rather than by cell death. Cortical cells are known to exhibit early patterns of diffuse or "exuberant" connectivity. For example, callosal neurons originate from the entire visual cortex in kittens, but are restricted to a specific area by adulthood (Innocenti et al., 1977; Innocenti and Caminiti, 1980). Similarly, projections from occipital cortex to the pyramidal tract are present in newborn rats but are absent in adults (Stanfield and O’Leary, 1985; Stanfield et al., 1982). Innocenti (1981) showed by means of injections of HRP and long-lasting fluorescent tracers in areas 17 and 18 of kittens that, although the cells labelled by this process are still present 2 months later, their callosal axons become progressively more restricted with age. Re-injection at 2 months with a second tracer shows that at this age only cells near the 17/18 border, parts of 19 and of suprasylvian cortex are double-labelled by retrograde transport. Similar experiments on the transient pyramidal tract projection in rats (Stanfield and O’Leary, 1985; Stanfield et al., 1982) and hamsters (O’Leary and Stanfield, 1986) show a complete elimination of corticospinal axons from occipital cortex without the death of the cortical cells.

Thus, early "errors" in connectivity in visual cortex (as well as in other cortical areas; see Ivy and Killackey, 1982) found to date are eliminated, not by the loss of the cells, but by retraction of collaterals. Presumably the cells are sustained by collaterals projecting to other, permanent targets. It is not known if these sustaining collaterals are present before collateral elimination occurs, or what factors trigger the collateral withdrawal. The results suggest that error correction is not a major factor in the normal cell death seen in the cortex.

2.6.3.2. Target availability

Another function of cell death in noncortical systems is the matching of afferent and target populations (Hamburger and Levi-Montalcini, 1949; Hollyday and Hamburger, 1976; Pilar et al., 1980; O’Leary and Cowan, 1984; but see Lamb, 1984). Studies on the effect of target removal on cortical cell survival are rare. Ramirez and Kalil (1985) have demonstrated that neonatal lesions of the pyramidal tract in the hamster have no effect on the final number of pyramidal cells in motor cortex, although they did observe that the somata of target-deprived cells were smaller in size than normal. This is apparently not due to the selection of a population of cells with smaller somata; rather a large-celled population,
which in the adult projects to the spinal cord, is arrested in its growth (but see Tolbert and Der, 1987).

We have explored target dependence of visual cortical cells in the hamster (Pallas et al., 1988). Neonatal unilateral deletions of the superior colliculus, a major target of layer 5 pyramidal cells in the primary visual cortex, were made to assess the effects of target loss on cortical cell death. The incidence of pyknotic cells during the major period of cell death (postnatal days 5–10) and in adults was monitored, as well as the total number of cortical cells in layer 5 and in all cortical layers combined. The target deletions were found to have no effect on either cell death incidence during development, or on final cell number, either in layer 5 alone or in all cortical layers combined. In addition, there was no effect on soma size, in contrast to the results of Ramirez and Kalil.

Thus, at least for cells in layer 5, availability of the primary target, the superior colliculus, does not influence cell death, indicating that the primary purpose of cortical cell death is not population matching.

The independence from the primary target does not imply, however, that cortical cells do not require some minimum amount of target space. In fact there is evidence that the reason cortical cells are not affected by target deletions is that they have sustaining collaterals in other targets. For example, many cells in layer 5 of area 17 send collaterals to both the pontine nuclei, the lateral posterior nucleus of the thalamus (LP) and the superior colliculus. In the rat, Hallman et al. (1988) have reported that at least 60% of corticocortical cells also project to the pons, as shown by double-labelling studies. Baker et al. (1983) obtained a similar result in the cat using antidromic activation. Klein et al. (1986) could antidromically activate 50% of corticocortical cells from LP in the hamster thalamus. It is not known how many collaterals (synapses) are required for survival, and whether this differs in different cells. In addition, some collaterals may be more essential for cell survival than others (Tolbert, 1987). Perhaps at least some of the cells that normally die during neocortical development are those which did not establish any permanent targets. Thus the extreme case of collateral elimination results in cell death. There is no evidence that cells can survive without some minimal amount of axonal arbor and thus target space.

Another study in our laboratory demonstrated the effect of loss of callosal targets on survival of cells in several cortical areas, including the 17–18 border (Windrem et al., 1988). Callosal projections were prevented by the insertion of a barrier along the cortical midline in neonatal hamsters. This target loss had no effect on cell survival (number of neurons/unit column) either in the callosally-projecting layers (II–III and V) or in the entire cortical column. These results are in agreement with the superior colliculus ablation study and suggest that target matching is not the function of cortical cell death.

2.6.3.3. Afferent availability

Section of the corpus callosum also eliminates a significant portion of the afference to cells in cortical layers II–III and V. Thus the results discussed above also indicate independence between cortical cells and their callosal inputs. Again, the reason for this independence between cortical cells and their inputs and outputs is suspected to be the presence of sustaining collaterals. Evidence that the callosally-projecting cells also have ipsilateral collaterals was presented above (Innocenti, 1981; Innocenti et al., 1986).

Other sources of afference show a more substantial effect. Lesions of thalamic input nuclei have a strong effect on cortical cell survival. Windrem and Finlay (1985, 1986) made unilateral thalamic lesions in neonatal hamsters and measured resulting cortical cell numbers in the cortical projection areas of the thalamic nuclei affected by the lesions. Cell numbers were measured in adults as well as in postnatal day 7 (P7) animals, just after the cessation of migration to the cortex. No significant differences were found in cell number per cortical column or in the laminar composition of the cortex in the P7 animals. This confirms that the cortex was not directly damaged by the early thalamic lesions, and also demonstrates that the thalamus is not required for the last phases of cortical cell generation or for successful migration to the cortex. By adulthood, however, there was a significant reduction in the total number of neurons per unit cortical column (by a mean of 13%). This difference was due to the absence or substantial reduction of an identifiable layer IV and reductions in layer VI. Only layer V, which is neither afferent nor target for the thalamus, was unaffected. However, the amount of increased cell death was not enough to account completely for the loss of layer IV. It appears that some of the cells which are normally destined for layer IV according to their birthdate may not become stellate cells but instead have a pyramidal morphology and reside in layer II–III (Windrem and Finlay, in preparation). An alternate explanation is that the lack of thalamic afference causes an increase in death of presumptive layer IV cells which is compensated by an increased survival of layer III cells.

Rakic (1988) has done a similar study in monkeys, where a reduction in the number of thalamic afferents to visual cortex was made by removing both eyes. This reduces the number of LGN cells by at least 50% if done by embryonic day 60. The result is a reduction in the size but not the thickness of area 17, which Rakic interprets as indicating that the number of proliferative units has decreased as a result of afferent deprivation without decreasing the number of divisions of each proliferative unit. However, the number of proliferative units is set before migration, which is before the thalamic afferents can come into contact with the cortical cells. Thus, it is difficult to understand how the afferents could influence the original number of units, or even the number of units which survive to proliferate. In light of this difficulty, Rakic raises the possibility that some units originally destined for area 17 are respecified into area 18 units by accepting the inputs typical of area 18 rather than those for area 17, which in this experiment have been largely removed by enucleation.

Thus, although cortical cells in layers II and III are independent of their callosal afference and targets for survival, and layer V cells are independent of at least some of their subcortical targets, thalamic afferents
are of critical importance—in the pattern of cell death, the formation of layer IV, and perhaps in the total size of cytoarchitectonic areas. The question remains why it is only layer IV cells that are uniquely dependent on their connectivity patterns for survival.

We can conclude that the primary reason cell death occurs is not for error correction and target matching. However, thalamic afference is important in controlling the pattern of cell death. How is this control achieved?

2.6.3.4. Generation of cytoarchitectonic differences (sculpting)

The increase in thickness in the binocular portion of area 17 discussed earlier is due primarily to an increase in layers II–IV, but especially in layer IV. However, there are differences between all cortical areas in the number of cells per column in layer IV, which are compensated for in all but the binocular portion of 17 by changes in layers III, V and VI (Rockel et al., 1980; Peters, 1987). Layers I and II remain uniform between the different areas.

The magnitude of the difference in thickness of layer IV in different cortical areas is correlated with the amount of thalamic input an area receives. Those areas of cortex which do not receive direct thalamic afference (such as the medial wall) are those which are agranular in appearance (meaning that they have a reduced or absent layer IV). Conversely, areas which receive heavy thalamic input (such as primary sensory cortices) are distinguished by their thick granular layers. The question remains, however, regarding what developmental events control these differences.

Windrem et al. (1985, 1986) have shown that early removal of thalamic afference leads to a decrease in the final number of non-pyramidal cells. It thus seems possible that the thalamic afferents initiate the differentiation of migrating neurons into non-pyramidal or granule-type cells. During the time that presumptive layer IV cortical cells are migrating along the radial glia, they can potentially come into contact with the thalamocortical afferents which reside under the cortical plate at this time (Lund and Mustari, 1977, Rakic, 1977, 1983; Shatz and Luskin, 1986). Windrem and Finlay (1985, 1986) propose that the cells which are generated during this time are pluripotent and can form either layer II–III or IV. If they do not come in contact with thalamic axons, they would express a pyramidal morphology and form layer II–III, but the contact with the thalamic axons would specify their differentiation as non-pyramidal (star pyramids or stellate cells) layer IV cells. Then during the period of normal cell death which follows migration (Finlay and Slattery, 1983; Heumann et al., 1980; Peters, 1987). Layers I and II remain uniform between the different areas.

The manipulation of relative activity levels often results in local alterations in the convergence ratios between afferent axons and postsynaptic neurons. Wiesel and Hubel (1963, 1965) studied the effects of visual deprivation on the physiological properties of cells in the LGN and striate cortex in kittens 9 weeks of age or older. Monocular deprivation had no
apparent effect on most cells in the LGN in that they showed normal receptive field sizes and configurations, although they were somewhat less excitable than normal and their somata were smaller. More recent studies have revealed that monocular deprivation does have an effect on Y cells, however. Sherman et al. (1972) have shown that there are fewer Y-type cells in the deprived laminae of the LGN compared to both normal and non-deprived laminae (although this could be due to electrode sampling error given that the deprived somata are smaller than normal). Physiological changes in the Y cells include poor responsiveness and somewhat larger receptive fields (Krantz et al., 1978). Morphologically, it has been observed that Y-cell axons from the deprived eye have shrunken terminal arbors in the A laminae and in MIN (Sur et al., 1982). The Y cells establish their terminal arbors later than the X cells (Sur et al., 1984), and their lack of correlated activity under conditions of monocular deprivation may prevent them from pruning back the arbors of the X cells (Garraghty et al., 1986).

At the cortical level, kittens monocularly deprived from birth of patterned light exposure were apparently blind in the deprived eye, despite what was reported by Wiesel and Hubel (1963, 1965) as the relative normality of geniculate cell responses. Only one cell out of the 84 recorded could even be driven by the deprived eye and it showed no orientation preference and was very sluggish. Responses of cells driven by the non-deprived eye were normal. There was an increased incidence of cells which could not be driven by either eye. Substantial projections to striate cortex from the deprived laminae of LGN remain; however, these inputs are largely below threshold (Kratz et al., 1976). The effects can be lessened by normal visual experience prior to deprivation, and they exhibit a critical period; deprivation in adults has no effect. These results have been confirmed repeatedly (e.g. Shatz and Stryker, 1978; Singer, 1977; Wilson and Sherman, 1977).

Binocular deprivation also decreases the responsiveness of cortical cells, indicating that some non-competitive effects can occur as well. In lid-sutured cats, which are deprived of pattern vision but not deprived completely of light, fewer cells are responsive to light, and receptive fields are larger with more diffuse borders (Hubel and Wiesel, 1963; Singer and Tretter, 1976; Watkins et al., 1978). Dark-rearing also decreases the responsiveness of cortical cells to light, but field sizes remain normal (Cynader et al., 1976; Leventhal and Hirsch, 1980).

These results taken together indicate that monocular deprivation causes the disruption of retino-geniculate and geniculocortical connections from the deprived eye that were initially present at birth, without any effect on the responses of cells driven by the non-deprived eye. Because binocular deprivation causes a much less severe deficit than monocular deprivation, it can be inferred that it is in large part competition between projections from the two eyes that restricts the extent of the geniculocortical fibers' arbors. Any manipulation which changes the balance of activity between the two eyes will put the deprived eye at a disadvantage in "capturing" synaptic connections. Conversely, any manipulation which affects the activity level of the two eyes equally has lesser effect. Further evidence for the role of activity comes from binocular TTX injections, which prevent the formation of ocular dominance columns (Stryker and Harris, 1986).

Although monocular deprivation has been studied in detail, the consequences for afferent/target convergence ratios have not been addressed. For example, the projections of the deprived eye reflect a greater reduction in Y-cell than in X-cell terminals (Shatz and Stryker, 1978), and terminals of the non-deprived eye expand in layer IV of striate cortex so that they contact more target cells (Hubel et al., 1977; Shatz et al., 1977; Shatz and Stryker, 1978; LeVay et al., 1980). However, there is no apparent increase in the receptive field sizes of the cortical target cells receiving input from the non-deprived eye (Wiesel and Hubel, 1963). It would be of interest to know how this lack of change is achieved.

3.2. EFFECT OF DECREASED AFFERENCE/EXCESS TARGET ON PHYSIOLOGY

Rhoades and Chalupa (1980) have studied the effect of monocular enucleation in neonatal hamsters on receptive field properties of visual cells in the superior colliculus of adults. This manipulation leads to an expansion of the ipsilateral retinotectal projection, which is normally restricted to rostral tectum, over the entire tectum. They found that the receptive field properties of cells in the colliculus contralateral to the remaining eye did not differ from normal. However, several marked changes were observed in the properties of cells ipsilateral to the remaining eye. Receptive fields of these cells were abnormally large, and the field size was inversely correlated with the density of the ipsilateral retinotectal projection as determined by anterograde transport of tritiated proline. This change is particularly informative, as field size probably reflects the amount of convergence from the retina. Direction selectivity and surround suppression were rarely observed, in contrast to normal animals. The responsiveness of the cells in general was also related to the density of innervation.

Anatomical results obtained by Wikler and Finlay (1984; in preparation) are useful in interpreting the physiological results described above. They demonstrated a 30% decrease in synaptic density with the relative increase in target area caused by the monocular enucleation. The afferents, while able to expand their terminal arbor to some extent, apparently cannot increase the number of synapses enough to innervate the excess target up to its normal synaptic density. This occurs despite a 2-fold increase in tectal cell death in the ipsilateral tectum. Thus, the expanded receptive fields in these cells could be explained by increased branching of the afferents due to a decrease in competition for target sites. The absence of direction selectivity and surround suppression may indicate disruption of the normal pattern of inhibitory connections, but could also be due to decreased excitability. Because the innervation of each target cell is reduced, some decreases in excitability would be expected.

Monocular enucleation in kittens results in the
contralateral and ipsilateral LGN being innervated completely by the remaining eye in the adult. White et al. (1987) have studied the functional consequences of this manipulation by recording from single cells in the A layer of the LGN in these animals. They examined several characteristics of the receptive fields of these cells, including spatial resolution and the size and shape of the field. They found that LGN-X cells had larger receptive fields than normal and lower spatial resolution. The authors suggest that these differences could result from an induced mismatch between retinal ganglion cell afferents and LGN target cells resulting in changes in the pattern of afferent arborization. Garraghty et al. (1986) have shown that X and especially Y retinogeniculate afferents have a much more extensive arbor in cats enucleated at birth, supporting this interpretation.

They have postulated that X cells remain fairly restricted to their eye-specific laminae, and Y cells expand into the deafferented laminae. Because the excess target availability decreases the amount of competition between the X and Y cells within a lamina, both types of cells can expand their arbors. It should be noted that the enucleation-dependent expansion of X and Y arbors exhibits a critical period. Cats enucleated at E23 (Sretavan and Shatz, 1986; Garraghty et al., 1988) show no change in X and Y arbor size.

A different result was obtained by Shook et al. (1985) when they undertook a study of the physiological effects of monocular enucleation in the cat on visual cortical cells. Kittens were enucleated in utero at least 2 weeks before birth. Cortical units were then recorded in area 17 of adult cats. All cells were driven well by the remaining eye, in contrast to the lack of responsiveness observed in some ipsilateral SC cells in hamsters (Rhoades and Chalupa, 1980). However, the cells did show a marked difference from normal in the size of their receptive fields. Field size in the monocularly enucleated cats is smaller than normal (x = 1.76 degrees vs 2.67 degrees), in contrast to the results from retinocollicular connections in monocularly enucleated hamsters and retinogeniculate connections in cats. In both these species, monocular enucleation leads to an increased number of surviving retinal ganglion cells in the remaining eye. Shook et al., suggest that increased dendrodendritic competition between neighboring ganglion cells might result in smaller dendritic trees and thus contribute to the reduced field size. However, it is difficult to explain how increases in LGN cell field size can occur simultaneously with decreases in cortical cell field size. Perhaps the difference in time when the animals were enucleated plays some role. It is also possible that changes in intracortical inhibitory circuitry are responsible. More anatomical information is needed to interpret these results, but future work on this system could be very informative.

Unlike the kitten which has a large degree of binocular overlap and thus a significant ipsilateral retinogeniculate projection, the retinogeniculate projection in the rat is largely contralateral. Monocular enucleation in the rat results in an expansion of the ipsilateral retinogeniculate projection. Fukuda et al. (1983) found that physiological responses of P (parvocellular) cells in the contralateral LGN do not differ compared to samples from normal animals. However, several differences were seen in the ipsilateral P-cell population in the enucleated rats as compared to normal. Receptive field center sizes were significantly larger in LGN cells ipsilateral to the remaining eye. It was hypothesized that disruption of the normal one-to-one connection between RGCs and LGN cells could explain the change in receptive field size.

In summary, challenges to the afferent/target matching process in the case of increased target area (monocular enucleation) cannot always be compensated for. In rat and cat LGN and in hamster SC, the afferents cannot expand enough to fill the excess target even by increasing their extent of branching, despite some documented increases in cell survival in the ipsilateral eye when competition from the contralateral eye is removed, and some increases in cell death in the underafferented target. The increased branching leads to increases in receptive field size, perhaps because more afferents synapse with each target cell. Thus, there is an upper value for target size beyond which the afferents cannot expand their arbor enough to fill the target adequately to maintain field size. The extent to which the afferents can expand their arbor in turn determines cell survival in the target, as shown by the increased amount of tectal cell death in enucleates. These two mechanisms serve to regulate afferent/target cell ratios with a certain range. However, in cat cortex, decreases in field size result from monocular enucleation. This result is difficult to interpret without further information.

### 3.3. Effect of Excess Afference/Decreased Target on Physiology

What is the response of the visual system to an increased number of afferents at the periphery? Does this result in increased survival of target cells, and thus a concatenated increase in the size of all visual nuclei central to the increase in afference? If not, how are the excess afferents accommodated functionally and anatomically?

These questions have been addressed only rarely in the mammalian visual system (Murphy and Kahl, 1979). Our studies using the retinotectal system of the hamster (Pallas and Finlay, 1986, 1987, in press) provided some interesting results that are relevant in this regard. Partial unilateral tectal ablation in neonatal hamsters results in a compression of the entire contralateral visual field onto the remaining tectal fragment (Jhaveri and Schneider, 1974a; Finlay et al., 1979a).

Retinotopic order is preserved in these animals, with the compression of the central nasal visual field being somewhat less than that in the far periphery (Finlay et al., 1979a). Multunit evoked potentials indicate that more retinal area is represented at each location in the superior colliculus as well. Wikler et al. (1986) found only a minor increase in cell death in the retina with the neonatal partial tectal ablations, and no change in cell death within the superior colliculus (SC). Thus, for a lesion of the caudal half of the colliculus, approximately twice the normal number of retinal ganglion cells are potentially available to each tectal cell. This preparation provides a convenient experimental system in which to study the
We studied the effects of the early lesions (removing 20–75% of the SC, mean = 38%) on several different physiological properties in the tectal target cells, including receptive field size. Responses of cells from lesioned animals were compared to those recorded from normal and sham-operated animals.

In lesioned animals with compressed visual maps, an increased area of visual field is represented per unit of tectum. One might expect then, that individual SC cells would have increased receptive field sizes as a result of the excess afferents (compare Fig. 3A and Fig. 3B). However, our results show that this is not the case. Receptive field size was not significantly different between lesioned and intact animals. This result is in contrast to the results of multiunit recordings (Finlay et al., 1979a), which showed increases in field sizes proportional to the size of the lesion. Other receptive field properties, such as velocity and size tuning, were also unaffected.

These results suggest, then, that the increased convergence of the visual field onto the SC is not reflected in increased convergence at the level of the single cell. This would mean that the model shown in Fig. 3B is incorrect. How then can the two results, increased field size with multiunit recordings and no change in field size with single unit recordings, be reconciled? We have proposed the model shown in Fig. 3C as a possible interpretation of the results. The model involves a simple arbor pruning of the RGC's which maintains the original number of RGC's projecting to the tectum without a change in synaptic density. This interpretation is supported by preliminary evidence from Wikler and Finlay (1984, in preparation) that synaptic density remains constant in the SC of hamsters with early partial tectal ablations. The model depicts a 50% ablation; in this case, each tectal cell receives input from the same number of RGC's as usual and these RGC's cover the same amount of retinal area, but each RGC has half its original arbor. The model does not exclude the possibility that RGC collaterals project to alternate targets, however. Multiunit recordings (e.g. recording from two adjacent SC cells in the model) show an increase in field size, but single unit recordings do not.

There is some evidence for increases in retinal projections to alternate targets in animals with early partial tectal lesions. Udin and Schneider (1981) reported a decline in the density of retinal ganglion cells projecting to the tectum in hamster with early lesions. Crain and Hall (1980a,b) demonstrated an increased projection to the LP nucleus of the thalamus following partial tectal lesions in hamsters. However, the extent of the projection to alternate targets was not enough to account for the amount of target loss, suggesting that some combinations of arbor reduction and projection to other targets may be occurring. To address this point, we are now conducting a study in which the density of RGC projections to the tectum is measured with varying lesion sizes. Perhaps a reduction in arbor is the response of the cell to small lesions, but if the amount of available target drops below a threshold amount, projections to other targets occur (Fig. 4).

In summary, the hamster retinotectal system is remarkably resistant to increases in afferent availability in terms of its physiological properties. This resistance appears to arise as a result of alterations in circuitry which compensate for increased afference in such a way as to maintain receptive field properties.

What prevents the excess afferents from superinnervating the tectal fragment? Or conversely, what prevents the tectal targets from accepting more than their usual number of inputs? Our results suggest that the target cells can be quite selective about their inputs; even in the presence of excess afferents, the number of afferents innervating a single tectal cell and the amount of retinal area they represent is held at the normal value. This could be explained by an activity-dependent sorting mechanism that is specific enough to select down to the single cell level. That is, when confronted with a larger number of potential inputs with less-correlated activity patterns, the sorting mechanism does not adjust its selectivity. In our experiments, each tectal target cell could potentially be innervated by twice the usual number of afferents, which would have half the overall amount of coincidence in their activity patterns. Instead, only the usual amount of visual field is represented in each target cell, by the same number of innervating ganglion cells as seen in the intact state.
This explanation predicts that there will be a limit to the amount of target that can be deleted while still maintaining receptive field properties in their normal state. In accordance with this prediction, we (Finlay et al., 1979a,b; Pallas and Finlay, 1986, 1987, in press) have observed, with very large lesions of the superior colliculus, that only temporal retina is mapped onto the SC. We suggest that this reflects the limit to the amount of plasticity the system can exhibit with increasing amounts of target loss. If nasal ganglion cells cannot obtain enough target within the tectum, they drop those collaterals and/or project elsewhere. Thus, the solution of this particular system to an extreme lack of target is to make only a partial topographic map (Fig. 3).

From these results, it is apparent that another constraint operating is that of the conservation of a minimum amount of axonal arbor by each presynaptic axon (see Devor and Schneider, 1975). The results from the studies of monocular enucleation suggest some additional constraints. In cases where afferents are depleted, the target will accept afferents which are spread out over a wider area of visual field (indicated by increased field sizes). Thus, there seems to be a two-stage selection process: when afferents are in short supply, they can spread over larger distances in the target because of decreased competition for terminal space, and the target cells operate as if they must accept whatever afferent input they can obtain, regardless of the absolute amount of correlation in afferent activity patterns. One does not often see receptive fields that are patchy, however, so there must be some constraint that maintains nearest neighbor relations between the inputs. When afferents are more numerous than usual, a second stage of selection operates that sorts inputs on the basis of activity-dependent sorting, and target cells will not accept other than the normal amount of coincidence.

What consequences does only an upper limit on convergence have for evolutionary change in visual systems? When more afferents are supplied as in a partial target deletion, the target will not accept them and circuitry is rearranged in order to maintain receptive field properties. Thus one can postulate that a mutation which increased the number of afferents could be compensated for. When more target is provided as in monocular enucleation, there is an increased sparing of cells in the remaining retina as the retinal ganglion cells spread to innervate the entire cortex. Rakic (1985) has found that vernier acuity (which is thought to depend on the visual cortex; Barlow, 1978, 1981) increases following monocular enucleation in monkeys. Such increased computational resources for a defined sensory input, as evidenced by increased vernier acuity, could provide the evolutionary pressure for increasing encephalization. However, as other experiments described above show, monocular enucleation also can result in decreased synaptic density, increases in receptive field size in the target, and erratic responsivity of the cells. These results are not consistent, and it is not yet clear when excess target is advantageous and when it is pathological. It is also unclear whether reconciliation can be made between these results and the trend toward encephalization over evolutionary time.

4. SUMMARY AND OVERVIEW

4.1. What is the Function of Cell Death in the Developing Visual System?

Cell death has now been shown to have multiple functions in the developing visual system. However, an exhaustive list of these functions, with generous estimates of their total numerical contribution, does not satisfactorily account for more than half of the total estimated cell loss. This situation is quite comparable to what has been observed in the spinal cord: a documented function is the numerical matching of motoneurons to target muscle availability (no other functions have been described). Yet, provision of excess target of any kind can only reduce naturally occurring cell loss to about half of its normal amount, and the function of the residual loss thus remains a mystery.

Taking the case of retinal ganglion cells, for which the most quantitative evidence is available, we know that 50–80% of ganglion cells are normally lost. Cell death participates in the correction of errors of early laterality (Insausti et al., 1984). Corrections of errors of laterality account for no more than 1–3% of normal cell death. In some animals, cell death prefer-
entially removes cells from the retinal periphery: in hamsters, this sculpting can account for no more than 10% of normal cell death. For target matching, the maximum induced sparing of cells after provision of excess terminal field is 30% in monkeys, but in every other animal, considerably less. For hamsters, the only species in which all of these factors have been estimated, totalling these sources of loss gives an “accountable” loss of about 25% in a total population loss of 50–60%

More cell loss can be accounted for in the correction of errors of topography (O’Leary et al., 1986; Catticas et al., 1987). O’Leary and colleagues estimate that large topographical targeting errors in the rat occur at about a rate of 12% and hypothesize that if short-range “errors” were included, the error rate could account for the entire population loss. We propose a reinterpretation: that cell death in developing mammals and birds is an epiphenomenon of the process of activity dependent sorting occurring within a finite period. Activity dependent sorting requires that “inappropriate” terminals be transiently removed from their terminal areas. By this sorting process, a fraction of neurons may be prevented, on a statistical basis, from maintaining a stable synapse. As activity dependent sorting ceases and connections are stabilized, some neurons may be caught without a terminal connection, much as in a game of musical chairs. Neurons thus losing their connectivity could be construed as making very local “errors” of connectivity in failing to gain a particular postsynaptic neuron, but it is the transience of the plastic state that defines them as error (Lamb, 1984). If activity is prevented, cell death can be prevented (Oppenheim, 1981; Fawcett et al., 1984; O’Leary et al., 1986). This argument is supported by the observation that in animals with an unlimited plastic period, such as the growing teleost retina, cell death has not been reported.

Given this hypothesis, the amount of cell loss seen in a particular structure in a particular species will be a combination of several factors. First, since the range over which an axon arbor may vary is apparently quite large, but with a defined minimum, the initial ratio of generated presynaptic neurons to postsynaptic neurons will specify where the system is located in its potential axon range. This in turn will specify (in part) the likelihood of failure to establish the minimum arbor, and the response of the system to afferent and target deletions.

Secondly, the number and nature of the axonal branches that a neuron possesses will affect the probability of the neuron’s survival. Assuming that the establishment of any branch is enough to constrain a cell, consider the following situation: a nucleus from which each neuron’s axons bifurcate to innervate two targets (for example, the hamster retina/lateral geniculate/superior colliculus system), compared to a nucleus in which the same number of neurons does not branch and contacts either one or the other target (for example, part of the cat retina/lateral geniculate/superior colliculus system). Suppose the probability of failing to establish a synapse in each target is 0.5, and that the probability of failing to establish a synapse in one or the other target is independent. The probability of any individu-
number of motoneurons produced is related to eventual muscle size. Sperry (1987) found a natural variation in body size in *Xenopus* tadpoles that was correlated with the number of motor neurons and muscle fibers in the lumbar lateral motor column system (L-LMC) after metamorphosis. He measured body size, motor neuron number, and muscle fiber number before, during, and after the period of natural cell death. Contrary to the size matching hypothesis (Hamburger and Oppenheim, 1982), the percentage amount of cell death in the motor neuron population was fairly constant (approximately 70%) regardless of the number of neurons prior to the cell death period or the number of muscle fibers. Thus it appears that there is a regulation of motor neuron production according to body size that serves to match target and afferent populations. In the visual system of amphibians, cell generation and early aspects of specification of cell type can be regulated by the cellular milieu such that more cells of a particular class will be generated if that class is experimentally depleted (Reh, 1989).

For mammals, there is evidence for gross allometric regulation of visual system size (reviewed in Wikler and Finlay, 1989). Eye size (diameter) is grossly correlated to body weight (Hughes, 1977) which is in turn correlated to brain weight (Jerison, 1973; Eisenberg, 1981). However, at any particular body size across mammals, there is a 3- to 5-fold variation in eye size and a similar variation in brain weight. The relationship of eye size to brain weight has not been described systematically, but the relationship is unlikely to account entirely for the 3-5-fold variation. Thus, gross allometric scaling is likely to account for some basic visual system scaling, but the residual variability is large.

There is little direct evidence for regulation of cell generation as yet in mammals, either in the retina (Beazley et al., 1987) or centrally (DeLong and Sidman, 1962). In general, therefore, given the gross allometric context, there is little evidence to suggest that a target amount of cell generation is regulated or defended as a developmental means for controlling convergence.

### 4.2.2. Presynaptic axon arbor size

#### 4.2.2.1. Afferents

Afferents are generally in abundance, and targets are generally saturated with inputs. Deletions of afferents must therefore be fairly large to have any significant effect on target cell survival (Fig. 2). Similarly, we have been unable to show that a developmental increase in input to a structure is matched by an increase in cell survival in that structure (Raabe et al., 1986; Wikler et al., 1986) or anything but a transient alteration in volume of neuropil (Wikler et al., 1986). Therefore, except in the limiting case of massive afferent deletions, target cell number is not matched to afferent cell number. Except for its role in establishing boundary conditions for cell survival, afferent cell number is not defended during visual system development.

#### 4.2.2.2. Presynaptic axon arbor size

Cells in the visual system can survive with wide variations in amount of axonal arbor, as was first implied by the monocular eye closure experiments of Wiesel and Hubel (1964) and more recently demonstrated directly by reconstruction of full terminal arbors (Garraghty et al., 1986). Numerous experiments (reviewed in Sections 2.1-2.6 and in Sections 3.1-3.6) show that afferents appear to saturate target space, both when the relative competitive ability of afferents is altered by alterations in activity patterns or when the number of afferents is changed by direct deletions or additions. When target space is scarce, as in the several target deletion studies we have described (Fig. 1), the cells do not die proportionally, but appear to survive with lesser arbor or find alternate targets to some lower limiting value.

Devor and Schneider (1975) have hypothesized a principal of conservation of axonal arbor. Two interpretations of this principle are possible, one interpretation concerning the developmental "behavior" of the cell, and the second concerning the survival requirements of the cell. For the developmental behavior of cells, conservation of arbor implies that a cell can in some way monitor or defend its total axonal arbor: if part of the dendritic tree is pruned back by lack of target space, other parts will sprout in compensation. The difficulty in establishing whether axons actually maintain their arbor in this fashion is the necessarily confounded nature of target availability manipulations in the richly interconnected visual system: most target deletion studies also deafferent alternate targets, and thus free synaptic space (e.g. Crain and Hall, 1980b).

Conservation of arbor might also mean that a certain amount of arbor is required for cell survival, and a particular arbor size is regulated and defended. Stated more simply, in this view, the minimum amount of arbor is equivalent to the maximum amount of arbor. While there are certainly upper and lower limiting values, as described above, it is clear that most cells that have been investigated can survive with several-fold variability in their terminal arbor size.

#### 4.2.3. Target availability

##### 4.2.3.1. Cell number

Afferent cell number has been shown to be linearly regulated to target availability over a substantial range in the neuromuscular system (Sperry, 1987; reviewed in Hamberger and Oppenheim, 1982). This type of singly targeted system thus has its cell number constrained by target cell number. Although similar quantitative studies have not been done for similarly connected pairs in the visual system, like the singly-targeted geniculocortical system, it is a reasonable hypothesis that such pairs would also match linearly.

For multiply targeted cells, such as most retinal ganglion cells in rodents, or subcortically projecting cells of the neocortex, the total number of retinal ganglion cells is not matched to the total number of target cells summed over all targets; for example, in rodents, the entire geniculate body can be removed without change in retinal cell survival (Perry and
4.2.3.2. Postsynaptic dendritic arbor size

Dendritic arbor size has been shown to be highly malleable in situations related to gross cellular activity or function (Greenough, 1984; Turner and Greenough, 1985; Coss, 1979, 1980) or other functional alterations such as hormonal state (Goldstein et al., 1988). Dendrites also appear to compete with other dendrites to establish arbors, and will increase their size if competition is reduced, up to cell-type-specific limiting sizes, and will decrease their size if cell density is made higher than normal (Perry, 1989; Leventhal, 1989).

There are several interesting cases where dendritic arbor size does not change. In three-eyed frogs (Constantine-Paton, 1982; Constantine-Paton and Law, 1978), the size of the doubly-innervated tectum does not increase as might be expected if arbor size were increased to accommodate the extra afferents. In our own work (Hatlee and Wikler, unpublished) dendritic arbors of developmentally hyperinnervated cells in the superior colliculus did not increase. In contrast, however, a report that hyperinnervation increased the dendritic arbors of Mauthner cells has recently been made (Goodman and Model, 1988). If, as is commonly believed from a wealth of evidence, axons compete for a limited amount of terminal space, it is a necessary assumption that axons do not then determine the amount of terminal space.

We have suggested that there may be an upper limit to the number of inputs accepted by a target cell. At a cellular level, a simple explanation for this is that if total dendritic arbor size does not change, there is no room for extra inputs. This mechanism has been suggested for both muscle cells and autonomic ganglia. Most muscle cells have only one endplate, but larger fibers can have two or three, and these are always separated by a minimum distance (Bennett and Pettigrew, 1975, 1976). In autonomic ganglia, the number of axons innervating the dendritic arbor is directly related to the size and complexity of that arbor. The cause and effect relationship is suggested by the fact that early in development, each postsynaptic cell is innervated by about the same number of axons regardless of its geometry, and these are later pruned back according to dendritic arbor size (see Purves, 1977, 1983, for reviews).

The distinction between the marked dendritic growth mediated by activity, hormonal state, and interactions with neighboring dendrites and the absence of dendritic growth to excess of afferents is interesting, and may provide a mechanism by which connectivity is regulated, but which can be reset under appropriate environmental or physiological conditions.
above and within small ranges of variability, such a cascade could not occur. The change in cell number will most likely be met with changes in the presynaptic axonal arbor of the lateral geniculate neurons, and perhaps, changes in the branching patterns of individual axons. Constraints on the number of inputs a postsynaptic cell will accept would insure that the system would remain physiologically stable over a wide variation in convergence ratios (Section 3.3).

4.3. SOME EVOLUTIONARY CONSIDERATIONS

What are the evolutionary implications of these constraints? First, the wide inter-species differences in ratios of cell numbers between interconnecting structures are easy to accommodate to the wide experimentally-induced variations in these same numbers in a single animal. Mapping rules which allow a wide variation in afferent arbor size and branching, but a limit on the number of separate afferents a postsynaptic cell will allow seem to permit a wide variation in developmentally stable systems. The developmental impermeability of the neocortex to deletion of its targets, perhaps due to its widely branching axons (Fig. 1), suggests a reason for the extreme variation in its size in various species. If major subcortical or intracortical target zones of the cortex can be deleted without modifying cell death in the existing cortex then, conversely, more cortex could be generated and remain viable even without corresponding increase in the volume of subcortical target zones.

Finally, the physiological experiments on the consequences of changes in convergence ratios reviewed here present a paradox. If a mutation occurs which increases the number of cells in the periphery, the excess afferents can be accommodated without affecting the function of the system adversely. An increase in the number of target cells, as seen in the experiments on monocular enucleation, has very damaging effects on the number of and volume of central nuclei. How the developmental mechanisms described here could be employed to make efficient use of the existing cortex then, conversely, more cortex could be generated and remain viable even without corresponding increase in the volume of subcortical target zones.

Afferents a postsynaptic cell will allow seem to permit a wide variation in afferent arbor size and numbers in a single animal. Mapping rules which allow a wide variation in afferent arbor size and branching, but a limit on the number of separate afferents a postsynaptic cell will allow seem to permit a wide variation in developmentally stable systems.

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REFERENCES


Chalupa, L. M. and Williams, R. W. (1984) Prenatal development and reorganization in the visual system of...


PETERS, A. (1987) Number of neurons and synapses in primary visual cortex. In: The Cerebral Cortex, VI.
Further Aspects of Cortical Function including Hippo-


Shook, B. L., Maffei, L. and Chalupa, L. M. (1985) Functional organization of the cat’s visual cortex after
CELL NUMBER CONTROL IN DEVELOPING VISUAL SYSTEM


WIKLER, K. C., PEREZ, G. and FINLAY, B. L. (Submitted) Neurogenesis in the gerbil retina: a comparative analysis of the effects of developmental duration on retinal conformation.


