## Conclusions

It is generally accepted from studies of neuronal plasticity that sensory input is critically important for normal development. The results of these studies in rats and to some extent those in man suggest that continued sensory input and perhaps continued use of the brain's functional capacity may be necessary for maintenance of an optimally responsive CNS in old age. A decrease in sensory input to the brain due to degenerative changes in the sensory organs or perhaps to profoundly restricted social contact which can accompany old age in man will be reflected in reductions in metabolism and blood flow in brain regions involved in processing sensory information. Over a long period of time this 'sensory deprivation' may result in morphological involution in some brain regions. If, however, vascular disease develops in cerebral vessels during senescence, the occurrence of age-associated degenerative changes is accelerated and may in fact be regulated by the intensity and the time course of the vascular changes.

## Reading list

1 Rossen, R., Kabat, H. and Anderson, J. F. (1943) *Arch. Neurol. Psychiatry* 50, 510
2 Klatzo, I. and Spatz, M. (1981) in *Cerebral Ischaemia in the Molecular Basis of Neuropathology* (Davison, A. N. and Thompson, R. H. S., eds), pp. 132–149, Edward Arnold, London
3 Patel, M. S. (1977) *J. Gerontology* 32, 643–646
4 Vitorica, J., Andrés, A., Satrústegui, J. and Machado, A. (1981) *Neurochem. Res.* 6, 127–135
5 El-Hassan, A., Zubairu, S., Hothersall, J. S. and Greenbaum, A. L. (1981) *Enzyme* 26, 107–112
6 Gibson, G. E. and Peterson, C. (1981) *J. Neurochem.* 37, 978–984
7 Zubairu, S., Hothersall, J. S., McLean, P. and Greenbaum, A. L. (1982) *Enzyme* 27, 130–136
8 Kety, S. S. (1956) *Res. Publ. Assoc. Nerv. Ment. Dis.* 35, 31–45
9 Frackowiak, R. S. J., Lenzi, G.-L., Jones, T. and Heather, J. D. (1980) *J. Computer Assisted Tomography* 4, 727–736
10 Corseillis, J. A. N. (1976) in *Greenfield's Neuropathology* (Blackwood, W. and Corsellis, J. A. N., eds), pp. 796–848, Edward Arnold Ltd, London
11 Birren, J. E., Butler, R. N., Greenhouse, S. W., Sokoloff, L. and Yarrow, M. R. (1963) *Human Aging: A Biological and Behavioral Study*, US Government Printing Office, Washington, DC
12 Gottstein, U. and Held, K. (1979) *Acta Neurol. Scand.* 4 (Suppl. 72), II–10
13 Kuhl, D. E., Metter, E. J., Riege, W. H. and Phelps, M. E. (1982) *J. Cereb. Blood Flow Metab.* 2, 163–171
14 Sokoloff, L. (1975) in *Aging* Vol. 2 (Gershon. S. and Raskin, A., eds), pp. 45–54, Raven Press, New York
15 Owen, O. E., Morgan, A. P., Kemp, M. G., Sullivan, J. M., Herrera, M. G. and Cahill Jr., G. F. (1967) *J. Clin. Invest.* 46, 1589–1595
16 Sokoloff, L. (1978) *Trends NeuroSci.* 75–79
17 Smith, C. B., Goochee, C., Rapoport, S. I. and Sokoloff, L. (1980) *Brain* 103, 351–365
18 Duara, R., Margolin, R. A., Robertson-Tchabo, E. A., London, E. D., Schwartz, M., Renfrew, J. W., Koziarz, B. J., Sundaram, M., Grady, C., Moore, A. M., Ingvar, D. H., Sokoloff, L., Weingartner, H., Kessler, R. M., Manning, R. G., Channing, M. A., Cutler, N. R. and Rapoport, S. I. (1983) *Brain* 106, 761–775
19 Sokoloff, L. (1966) in *Cerebrovascular Disease* Vol. XLI, pp. 237–254, Association for Research in Nervous and Mental Disease, Williams and Wilkins, Baltimore

*Carolyn B. Smith is in the Laboratory of Cerebral Metabolism, National Institute of Mental Health, Bethesda, Maryland, MD 20205, USA.*

# Fibre order in the pathways from the eye to the brain

## C. Walsh and R. W. Guillery

*Some topographic order has long been recognized among the fibres of the visual pathways, but the analysis of this order has varied, depending on the species, on the part under study (near the eye or in the brain), and on the point of view and the methods of the investigator. In some regions the fibres are arranged as a map of the retinal surface, in some the order is more readily related to time of arrival during development and in some the order is less easily read. Here we discuss the different interpretations, relate them to each other and to the developmental processes that produce a number of distinct visual field maps in the brain.*

## Historical background

The earliest descriptions of the orderly arrangement of fibres in the visual pathways were produced by clinical neurologists (see Ref. 1), who compared clinically definable visual field losses with post-mortem observations and showed a retinotopic organization in all parts of the pathways. These observations, supported by experimental anatomical evidence, were summarized in 1957 by Polyak[1] and still form the basis of the usual textbook scheme, in which each optic nerve has a topographical representation of its retina and the optic tracts each have two overlapping, in–register maps of the contralateral visual hemifield, one map coming from each eye.

The anatomical evidence available in 1957 was largely based on the Marchi method. Although the Marchi method was widely mistrusted and produced results which varied from no order at all in the rat[2], or a rough order in rabbit[3] and monkey[4], to a rigid order almost, but never entirely in accord with the schematic representations (see Refs 1 and 5), the textbook schema was accepted, probably because it fitted so well with developing knowledge of accurate central maps in the lateral geniculate nucleus and cortex, which were the focus of interest at the time. It is instructive to recognize that when the much more powerful method of Nauta became available in 1954, our concern was with the central relays; only a few

studies dealt with the pathways[6], and although these raised important problems about the textbook view, they were not generally perceived as seriously challenging it.

A third approach was used by sensory physiologists, especially George and P. O. Bishop[7,8] and Chang[9], who were searching for functionally distinct fibre groups and who distinguished three or more fibre classes on the basis of conduction velocities and, thus, fibre diameters in the cat. Their work and that of van Crevel and Verhaart[10] showed quite clearly that there is a significant change in fibre order between the optic nerve and the optic tract: whereas fibres of different diameter are mingled in the nerve, they are clearly segregated in the tract. If the textbook accounts had been correct for the cat, and the tract carried in register maps of two half nerves, then the marked rearrangement of fibre diameter classes would not have been possible. The problem was not addressed because the two sets of observations were never brought together by anyone attempting a general analysis of fibre arrangements in nerves and tracts.

Developmental studies have played a fourth role in establishing that order in the pathways and order in the terminal maps can be treated as two separate problems. At first, Sperry's demon-

stration[11], that orderly retinotectal maps can regenerate in spite of an apparently inappropriate fibre order in the nerve, was taken as evidence that fibre order in the pathways was not relevant for the development of central maps and, for a period, fibre order seemed of little interest. More recently, as the general applicability of Sperry's chemospecificity hypothesis was challenged, other explanations of central map formation were sought. It was argued that the pattern of axonal outgrowth through the pathways might provide sufficient clues for the formation of retinotopic maps, and a number of studies of the pathways have been undertaken. While some have made extravagant claims about the order in the pathways[12], collectively they have focused attention on the part played by fibre order and have helped to define what the fibre order actually is.

## Fibre order in the cat's optic nerve and tract

The fibre order maintained in the cat's visual pathways was recently tested in a simple and striking experiment[13]. Horton and colleagues made a small injection of horseradish peroxidase into the cat's lateral geniculate nucleus which produced retrograde labelling of eight near-neighbour retinal ganglion cells and their axons. As the axons entered the optic nerve they were close together, but on their way to the chiasm they became widely scattered. This evidence seems to stand in clear contradiction to the clinical evidence for retinotopic order (see above). While this apparent contradiction may reflect species differences, other experiments suggest that a retinotopic organization, definable in the nerve when many fibres are studied[14], is not seen when only a few fibres are traced. Clearly, clinical evidence concerns a loss of large populations of fibres, whereas Horton et al.[13] were studying a small number.

In the cat, then, there is a change of fibre order as the optic nerve is traced from the eye to the chiasm, and consequently, fibre order in the tract follows a set of rules which is distinct from those governing order in the nerve. This conclusion also emerges from a number of recent studies of non-mammalian forms.

## Fibre order in the non-mammalian optic nerve

Herrick[15] studied normal silver preparations from *Ambystoma,* in order to confirm Ströer's[16] earlier description of a precise retinotopic mapping all along the optic nerve of *Triturus.* Although Herrick traced axon fascicles from each retinal quadrant into the distal parts of the optic nerve, he could not confirm Ströer's results. He found instead, an extensive intermingling of fibres from different fascicles along the nerve. Close to the chiasm, a different set of fascicles emerged. The larger, older fibres which were identifiable before metamorphosis, apparently coming from all four retinal quadrants, could be traced into the deeper parts of the optic tract, while the smaller, younger, fibers were nearer the pial border. That is, in the nerve Herrick found a reorganization of the fibre order, and within the tract he saw an arrangement according to fibre diameter, which could be interpreted as representing the age of fibres.

A reorganization of fibre order has been described in the optic nerve of many different species, but the fibre order shows some variations between species. Recent studies of other amphibians and of fish have confirmed Herrick's observations of a change in fibre order along the optic nerve. Near the eye there are a variety of mappings of the retina[17–22], and these can be regarded as maps of the retinal surface, or of the order of ganglion cell production (a 'chronotopic map' see Ref. 23). The two are equivalent in these species because the retina adds new ganglion cells as concentric rings in a topographically precise manner[21,22]. Nearer the brain, the grouping of fibres according to age is maintained, but there is a mixing of fibres from within each annulus, so that the evident retinotopic order of the fibres is lost. Although it is difficult to arrive at a broad, inclusive generalization about fibre order in these several species, it is clear that there is a change in fibre order as the axons pass towards the brain.

## A generalization about the optic tract

In contrast with the optic nerve, the optic tract shows an organization that can be generalized for all vertebrates. Herrick's analysis, showing that the oldest fibres of the tract are the deepest, was experimentally confirmed[26], and is found in several non-mammalian species[18,23–25]. Age is rather accurately represented by the radial dimensions of the retina and in the tract the retinal rings are represented as layers parallel to the pia (see Fig. 1). Fibres from the four retinal quadrants are also segregated in the optic tract of non-mammalian vertebrates (Fig. 1) and the rough map

thus formed can be regarded as a precursor of the maps made by the axon terminals. In development, tract order does not depend on pre-existent terminal maps. Some aspects of the map are present when the first retinofugal fibres enter the tract, before the tectum is invaded[27] and, further, an early removal of the tectum, before it is invaded by the retinal afferents, does not change the fibre order in the tract[18].

The mammalian optic tract has been most closely studied in cats, in which, at first sight, the fibre arrangement looks extremely complex, quite unlike either the classical scheme or the non-mammalian pattern. However, some order appears if an analysis is made in terms of the several ganglion cell classes (indicated in terms of large and medium cells in Fig. 1). These classes are distinguishable by morphological and physiological criteria, which are well established and can be related to axon diameters and conduction velocities in the tract[28]. Torrealba et al.[29] studied the retrograde labelling of retinal ganglion cells after injections of horseradish peroxidase into parts of the optic tract, and showed several separate, overlapping rough retinal representations in the tract, each being contributed by one ganglion cell class.

These several maps can also be seen as representing the sequential order of arrival of retinofugal axons in the tract, with the oldest axons furthest from the pia (Fig. 1). However, the relationship is less evident than in frogs or fish because retinal development in mammals does not follow a strict central: peripheral sequence[30–34]. Rather, studies of ganglion cell 'birthdates', using ^{3}H thymidine, show that the several ganglion cell classes are produced as separate but partially overlapping, broad waves, each starting near the central retina and progressing towards the periphery[31–34]. The chronological relationships of these waves of cell production correspond to the spatial relationships established by their axons in the tract. For example, the medium sized β-cells are produced early and their medium caliber axons lie deep in the tract; the largest, α-cells are produced later and their large axons lie nearer the surface; the last wave of cell production includes mainly small cells (γ and ε; not shown in Fig. 1), and, correspondingly, many fine axons lie nearest the pia[29,31–33].

A more direct demonstration that the oldest fibres lie deepest in the tract has been obtained in ferrets, a close relative of the cat, with a comparable retino-
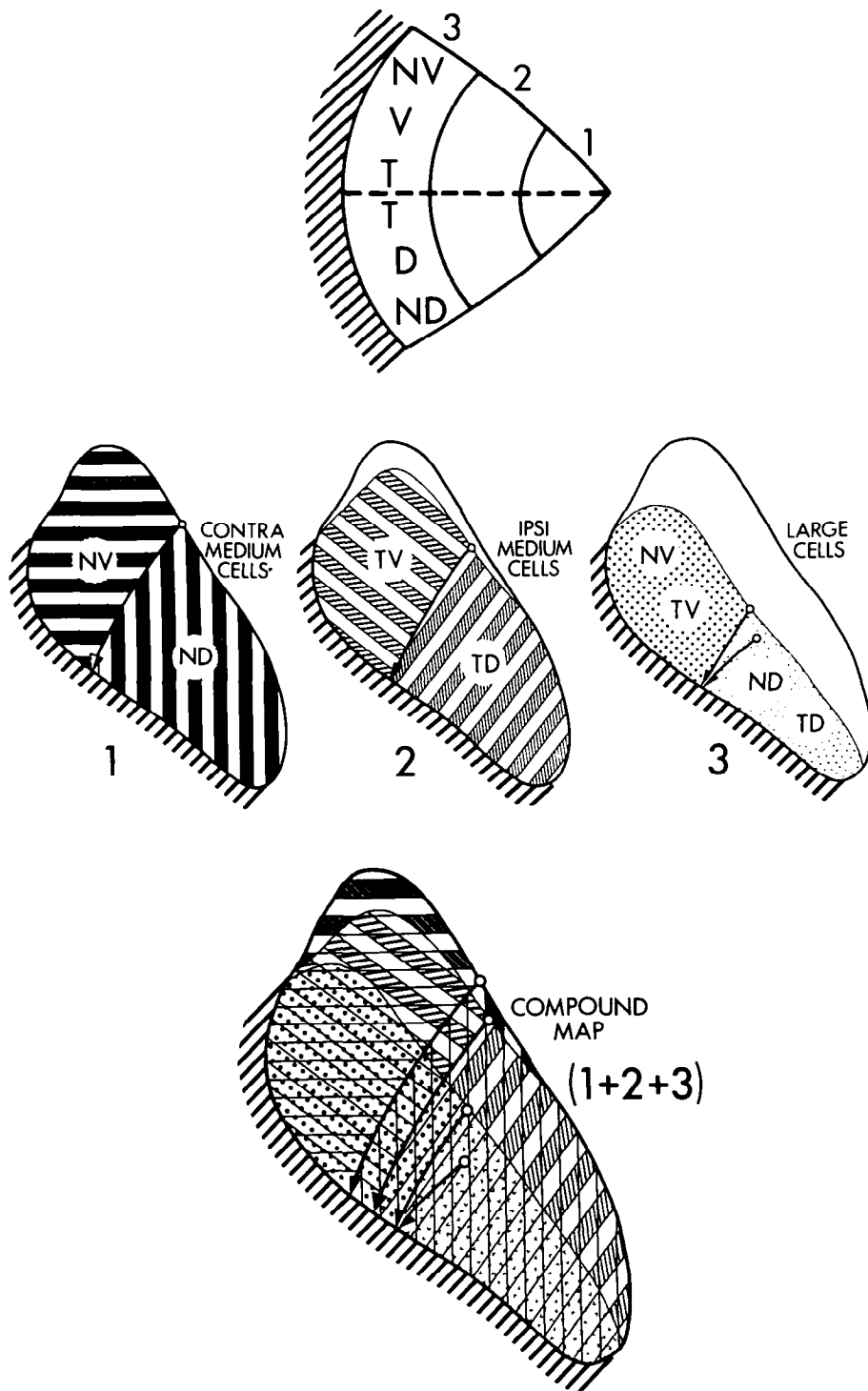
**Fig. 1.** *Schematic representations of fibre order in the optic tract in terms of the relative ages of the fibres and of their retinotopic arrangements.*

*The upper figure (adapted from Refs 18 and 26) represents the optic tract of Rana. D, V, T, and N show the positions of fibres from the dorsal, ventral, temporal and nasal retina respectively. The numbers indicate the central-peripheral order (1 being most central), and the relative age of the fibres, since the central fibres are the oldest. The youngest fibres always grow next to the pia (which is shown by oblique hatching to the left), displacing the pial surface as the brain grows and more fibres enter the tract.*

*The lower figures (adapted from Ref. 29) represent the cat's optic tract. Here a single section through the tract is shown four times. In sections 1, 2 and 3 the shaded portions show the distribution of different fibre components as indicated, each component being somewhat displaced relative to the others. Fibres from the medium sized contralateral ganglion cells appear to enter the tract earliest (1) and are then joined by fibres from medium sized ipsilateral ganglion cells (2) and by fibres from large cells (3), the crossed fibres being slightly displaced relative to the uncrossed fibres, as indicated by the two arrows in 3.*

*The central area of the retina is represented by a small circle in these figures, the horizontal meridian by an arrow. D, V, T, and N indicate parts of the retina as in the upper figure. The pial surface is to the lower left and, as in Rana, the oldest fibres are furthest from the pia.*

*The several components of the adult cat's optic tract are shown superimposed in the lowest part of the figure (1, 2 and 3), where one sees a record, rather like a geological record, of the sequence of the ingrowth of the fibres.*

fugal system. The oldest fibres can be preferentially labelled with axonal markers injected into one eye during the period of axonal outgrowth[35]. After short survival times (24 h), axons throughout the tract are labelled, but with longer survivals, the youngest axons, which were produced after the injection, carry no label and lie nearest the pia. These experiments have demonstrated the temporal sequence of tract production, and have also shown that tract order is present at an early stage, before the axons have entered the subcortical relays.

In the optic tract of cats and ferrets, then, as in non-mammalian vertebrates, the direction perpendicular to the pial surface represents the radial dimension of the retina. However, the topographic maps of the retina present in the cat's optic tract are not like those of fish or amphibians. Not only does each ganglion cell class in the cat have its own map, corresponding to its own wave of cell production, but the relationships established between the maps of the nasal and temporal retinae differ (Fig. 1). In fish and frogs, fibres from the retinal quadrants tend to be separated from each other. In the cat, the upper and lower retinal quadrants are also segregated in the tract, but in each tract the nasal quadrants from one eye and temporal quadrants from the other overlap, as though the maps of the retinae had been folded along the vertical meridian[29]. This agrees with the classical view of in–register maps of homonymous hemiretinae and corresponds to the terminal maps in the relays: in mammals that have significant binocular vision, the retina is not represented centrally as a single map of the whole retinal surface as in the non-mammalian tectum, but as two in-register maps of homonymous hemiretinae, each represented in a different layer or set of layers[36]. Again, the relationship between these hemiretinal maps can be represented by folding a schematic retina along the vertical meridian (see Fig. 1).

The maps in the optic tract can, therefore, be regarded as being anticipatory of the maps formed in the central relays: the maps that lie deepest in the tract also lie deepest in the relays[29] and the retinal quadrants are appropriately arranged.

## Developmental considerations relating to the differences between the optic nerve and tract

There are two possible approaches to understanding the differences between

the optic nerve and tract. One is to consider the growing axons in relation to their cellular environment, looking for the physical or chemical factors that influence the direction of axonal growth. The other is to take a more teleological view and consider that the development of nerve and tract differ because the sorting of fibres in the nerve must be appropriate for the chiasmatic segregation, whereas that in the tract must lead to an appropriate order of terminals in the relays. These are not opposing views. Rather, the relationships revealed by one approach may suggest mechanisms for solving problems raised by the other.

The first approach, of considering the relationships of the earliest axons, demonstrates two quite different cellular environments in nerve and tract. The nerve develops from the simple, tube-like eye stalk, made up of columnar cells. The early axons are embedded in individual cells, forming distinguishable bundles[37–40]. In contrast, the tract develops at the surface of the diencephalon, the axons relate to the outer processes of radial glial cells, at some distance from the glial cell bodies, and appear to be added in layers to the sub-pial surface. This method of adding fibres to the surface of a developing pathway may be quite common. It was described by His[40] in the spinal cord and more recently in other systems[41–42]. This surface addition, which may depend on the properties of the sub-pial surface, will naturally produce chronotopic maps. However, this pattern of growth must be supplemented or overruled by others wherever axons pass deep into the brain. Further, while surface addition can provide a basis for chronotopic order it does not provide a key to the orderly separate mapping of the retinal quadrants.

. The second approach, of considering the fibre segregation which must be produced in the adult, leads one to expect that nerve and tract must have a different order in any species having a significant partial decussation in the chiasm. It further provides a possible clue to understanding some of the differences between species in the optic nerve because there are major differences between species in the pattern of the chiasmatic sorting. In some, there is no chiasmatic sorting at all, but a complete crossing of the two nerves[5,20], in some only the axons from the nasal retina cross[1], whereas in many species one finds a complex intermediate situation: there is a population of ganglion cells with a complete decussation and another population of gang-

lion cells with a partial decussation[5,28]. Given these complexities, and given that the fibre order in the optic nerve may play a role in producing the chiasmatic segregation, as well as contributing to a segregation anticipatory of terminal order, it is not surprising that there are no simple generalizations about fibre order in the nerve.

### General conclusions

We have seen that a new interest in developmental problems has produced a new view of fibre order in the visual pathways. In its turn, knowledge of the fibre order can lead to a re-evaluation of some developmental problems. Currently a major focus is on the development of the pathways. However, there is no reason why the new views on fibre order should not, in turn, influence electrophysiological or clinical studies again. For example, once it is recognized that a large part of the cat's optic tract is free of α cell fibres, it becomes possible to consider making selective lesions to destroy, for a definable part of the visual field, some of the functionally distinct retinofugal cell types while sparing others. The possibility that lesions can destroy only some of the components arising from a patch of retina should be of interest to sensory physiologists and may also lead to a reconsideration of the clinical effects of partial lesions in the pathways.

### Reading list

1 Polyak, S. (1957) The Vertebrate Visual System (Klüver, H., ed.), 1, 1390, University of Chicago Press, Chicago
2 Lashley, K. S. (1934) J. Comp. Neurol. 59, 341–373
3 Brouwer, B., Zeeman, W. P. C. and Houwer, A. U. M. (1923) Schweiz. Arch. Neurol. Psychiatr. 13, 118–136
4 Brouwer, B. and Zeeman, W. P. C. (1916) Brain 49, 1–35
5 Guillery, R. W. (1983) in Contributions to Sensory Physiology Vol. 7 (Neff, W. D., ed.), pp. 39–73 Academic Press, New York
6 Hoyt, W. F. and Luis, O. (1962) Arch. Ophthalmol. 68, 94–106
7 Bishop, G. H. and Clare, M. H. (1955) J. Comp. Neurol. 103, 269–304
8 Bishop, P. O., Jeremy, D. and Lance, J. W (1953) J. Physiol. (London) 121, 415–432
9 Chang, H. T. (1956) J. Neurophysiol. 19, 224–231
10 van Crevel, H. and Verhaart, W. J. C. (1963)

J. Anat. 97, 451–464
11 Sperry, R. W. (1943) J. Comp. Neurol 79, 33–55
12 Horder, T. J. and Martin, K. A. S. (1978) Symp. Soc. Exp. Biol. 32, 274–358
13 Horton, J. C., Greenwood, M. M. and Hubel, D. H. (1979) Nature (London) 282, 720–722
14 Mason, C. A., Polley, E. H. and Guillery, R. W. (1979) Soc. Neurosci. Abs. 5, 795
15 Herrick, C. J. (1941) J. Comp. Neurol. 74, 473–534
16 Ströer, W. F. H. (1940) Acta Neur. Morphol. 3, 178–195
17 Fawcett, J. W. (1981) J. Embryol. Exp. Morphol. 65, 219–233
18 Reh, T. A., Pitts, E. and Constantine-Paton, M. (1983) J. Comp. Neurol. 218, 282–296
19 Scalia, F. and Arango, V. (1983) Brain Res. 266, 121–126
20 Scholes, J. H. (1979) Nature (London) 278, 620–624
21 Easter, S. S., Rusoff, A. C, and Kish, P. E. (1981) J. Neurosci. 1, 793–811
22 Bunt, S. M. (1982) J. Comp. Neurol. 206, 209–226
23 Dawney, N. A. M. (1979) J. Physiol (London) 296, 13–14P
24 Straznicky, K. and Gaze, R. M. (1971) J. Embryol. Exp. Morphol. 26, 67–79
25 Johns, P. R. (1977) J. Comp. Neurol. 176, 343–358
26 Gaze, R. M. and Grant, P. (1978) J. Embryol. Exp. Morphol. 44, 201–216
27 Holt, C. E. and Harris, W. A. (1982) Nature (London) 301, 150–152
28 Rodieck, R. W. (1979) Annu. Rev. Neurosci. 2, 193–225
29 Torrealba, F., Guillery, R. W., Eysel, U., Polley, E. H. and Mason, C. A. (1982) J. Comp. Neurol. 211, 377–396
30 Sidman, R. L. (1961) in The Structure of the Eye (Smelser, G. K., ed.) pp. 487–506, Academic Press, New York
31 Polley, E. H., Walsh, C. and Hickey, T. L. (1981) Soc. Neurosci. Abs. 7, 672
32 Walsh, C., Polley, E. H. and Hickey, T. L. (1982) Anat. Rec. 202, 198A
33 Walsh, C., Polley, E. H. and Hickey, T. L. and Guillery, R. W. (1983) Nature (London) 302, 611–614
34 Kliot, M. and Shatz, C. J. (1982) Soc. Neurosci. Abs 8, 815
35 Walsh, C. and Guillery, R. W. (1982) Invest. Ophthal. Visual Sci. Suppl. 22, 46
36 Walls, G. L. (1953) The Lateral Geniculate Nucleus and Visual Histophysiology, University of California Press, Berkeley and Los Angeles
37 v. Szilly, A. (1924) Z. gesamte Anat. I. Abt. 74, 1–230
38 Silver, J. and Sapiro, J. (1981) J. Comp. Neurol. 202, 521–539
39 Strongin, A. C. and Guillery, R. W. (1981) J. Neurosci. 1, 1193–1204
40 His, W. (1904) Die Entwicklung des Menschlichen, Gehirns, p. 28, S. Hirzel, Leipzig
41 Nordlander, R. H. and Singer, M. J. (1978) J. Comp. Neurol. 180, 349–374
42 Taylor, J. S. H. and Roberts, A. (1983) J. Embryol. Exp. Morphol. 75, 49–66

Dr Walsh and Dr Guillery are in the Department of Pharmacological and Physiological Sciences, University of Chicago, 947 East 58th St, Chicago IL 60637, USA.