We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter 12

Seeing with Two Eyes: Integration of Binocular Retinal Projections in the Brain

Tenelle A. Wilks, Alan R. Harvey and Jennifer Rodger

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/56491

1. Introduction

In the visual system, accurate representation of images throughout each stage of processing requires the maintenance of topography in different but interconnected brain regions [1]. Topographic organisation also allows information from both eyes to be precisely integrated, underpinning depth perception and interpretation of the visual world. In the absence of this organisation within and between eye-specific projections, visual information becomes scrambled within the brain and function is compromised [2,3]. Despite advances in recent years that have given insight into the mechanisms responsible for topographic mapping of visual projections within the brain, comparatively less is known about the mechanisms that underpin the integration of binocular pathways. The aim of this review is to summarise what is known about the developmental processes that establish topography in binocular projections in key animal models. We review experiments in mice that examine the development of binocular projections to the superior colliculus and address the role of molecular guidance cues. We will also describe experiments in Siamese cats that shed light on the organisation of binocular projections to the lateral geniculate nucleus and visual cortex. Finally, we will discuss this research in the context of early diagnosis and rehabilitation strategies of loss of binocular vision in humans.

We will first describe the development and organisation of contralateral (crossed) and ipsilateral (uncrossed) visual projections to the major visual brain centres: the superior colliculus (SC), dorsal lateral geniculate nucleus (dLGN) and primary visual cortex (V1), with focus on their integration in relation to visual space. We will then consider how topography is established in the ipsilateral retinocollicular projection; specifically we will review recent evidence for the role of axon guidance molecules in organising the ipsilateral projection [2,3]

INTECH
open science | open minds

© 2013 Wilks et al.; licensee InTech. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

in the context of early experiments which explored the role of the contralateral retinal projection in integrating binocular projections [4,5].

2. Visual system circuitry in the brain

Light casts an image onto the retina, is transduced into electrical signals by photoreceptors, and after intra-retinal processing the information is sent to the brain by the only efferent cells of the retina, the retinal ganglion cells (RGCs). Two of the major RGC outputs in the mouse are to the contralateral superior colliculus (SC) in the midbrain (the mammalian homologue of the optic tectum) and to the contralateral dorsal lateral geniculate nucleus (dLGN) of the thalamus. Neurons in the dLGN that receive retinal input then project to the ipsilateral primary visual cortex (V1). In addition, a subset of retinal ganglion cells project to the ipsilateral LGN and SC, approximately 3% of all RGCs in pigmented mice [6] and rats [7]. This circuitry is summarised in Figure 1. Our focus is the integration of ipsilateral and contralateral projections within the SC, LGN and visual cortex to provide the basis for binocular vision. This is key for processes such as depth perception and acuity in the frontal visual field. Other visual projections, although important in vision (reviewed extensively in Sefton et al., 2004), are not considered further here.

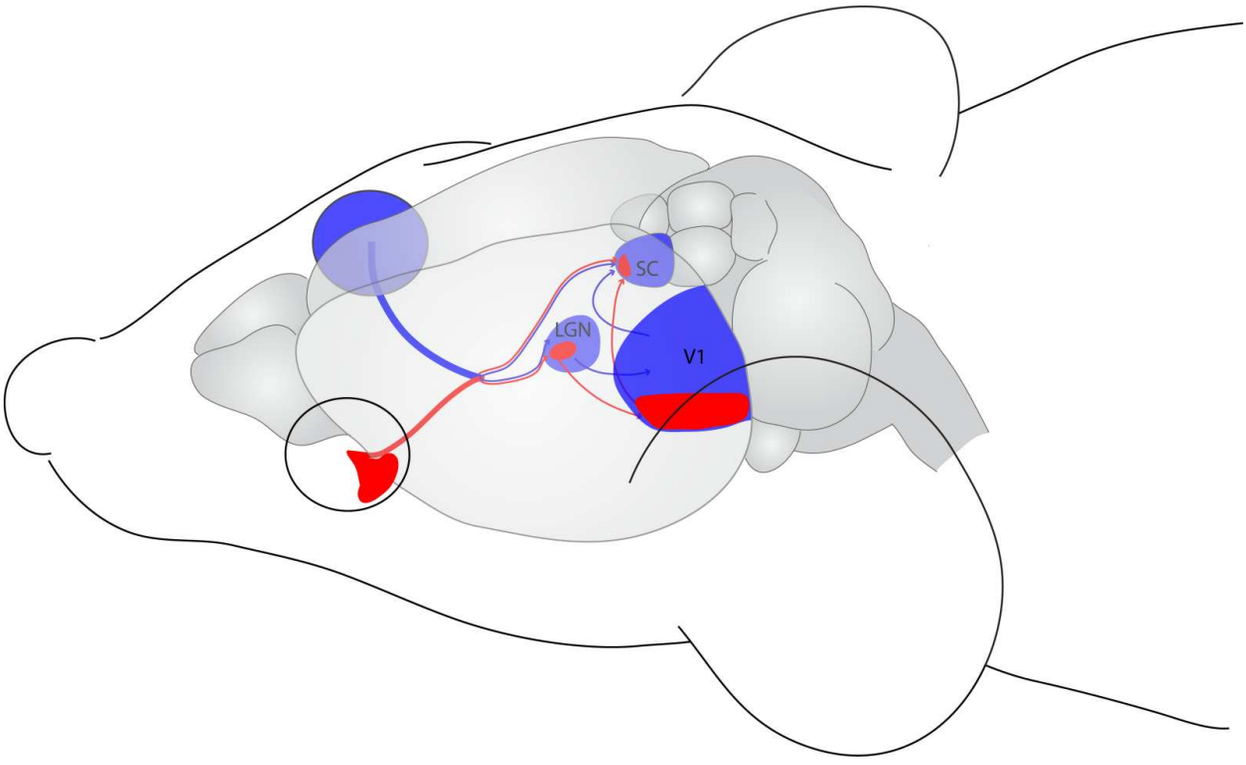


Figure 1. A schematic diagram of the main visual system circuitry in the mouse. dLGN= dorsal lateral geniculate nucleus, SC= superior colliculus, V1=primary visual cortex.

http://dx.doi.org/10.5772/56491

3. Retinal origin of ipsilateral projections

In most species, the number and distribution of ipsilateral RGCs within the retina correlates with binocular overlap and the orientation of the orbits [8]. Mice have laterally placed eyes and limited binocular vision; in pigmented mice, ipsilaterally projecting RGCs represent about 3% of the total RGCs population and are located in a temporo-ventral cresent, interspersed among a majority of contralaterally projecting cells [6]. Albino mice have an even smaller proportion with between 0.5-2% of the total RGC population projecting ipsilaterally [9]. This arrangement provides binocular vision in a 40-60^{o} strip within the superficial visual field [10, 11]. In normal cats, the proportion of ipsilaterally projecting RGCs is 17% [12], but is reduced to about 13% (variable) in Siamese cats [13]. By contrast, in primates (including humans) with frontally oriented eyes, about 50% of RGCs project ipsilaterally, and this figure is also thought to be reduced in albinos [14]. Unlike in mice, in cats and primates, there is a strict vertically oriented zone of transition at the area centralis/fovea between the purely contralateral projection found in nasal retina to the predominantly ipsilateral projection in temporal retina [13], although in Siamese cats, this zone of transition is shifted towards temporal retina [13]. In both species, the resulting binocular field is extensive and oriented towards the frontal field (120^{o} in cats, 140^{o} in primates; [8].

4. The horopter and Panum's fusional area

Stereopsis is the ability to perceive depth based on the differences between the information arriving on the two retinae [15], A key concept in stereopsis is that of the horizontal horopter [16], the collection of points in visual space at which objects are detected by corresponding (anatomically identical) points in the two retinae [17]. In species with frontally placed eyes and large binocular overlap the horopter takes the shape of a curved line running through the fixation point and fusion of images occurs only in a small volume of visual space around the horopter, known as "Panum's fusional area" [18]. Points in this area fall on slightly different retinal locations and thus lead to "retinal disparity", the basis of quantitative stereoscopic depth discrimination [17]. Species with frontally oriented eyes often have the ability to improve depth perception by fixating, or moving the eyes, so that the two foveae or areae centralis (the retinal regions of highest visual acuity in primates and cats respectively) are aimed at the object of interest [17]. In humans, fixation allows the perception of depth differences of up to 0.0014 degrees [17].

Binocular vision or stereopsis occurs when neural circuits use the disparity (parallax) information to compute depth [15]. In order for these computations to occur, the projections (ipsilateral and contralateral projections) from each eye that carry information from Panum's area must be brought together in the same brain regions and on to binocularly driven, disparity sensitive neurons, a phenomenon that occurs in steps as information is passed along the visual pathway via the dLGN [19].

5. Integrating binocular projections

There is an organisational challenge in the integration of ipsilateral and contralateral projections within visual brain centres. The eyes are reflectively symmetrical across the midline and RGCs map based on their position to the nose, therefore visual space is mapped in opposite orientations in each hemisphere (Fig 2A). For example, in the SC, nasal retina maps to caudal SC and temporal retina maps to rostral SC using gradients of ephrin guidance cues (amongst other molecules, discussed below; [20]. Therefore, in order to integrate the ipsilateral projection with the contralateral one and maintain a continuous and coherent representation of visual space, the ipsilateral projection must "flip" relative to the contralateral one (fig 2B; [5,6,21]. Note that this holds true not only for mice with laterally positioned eyes, but also for cats and humans with frontally positioned eyes [22].

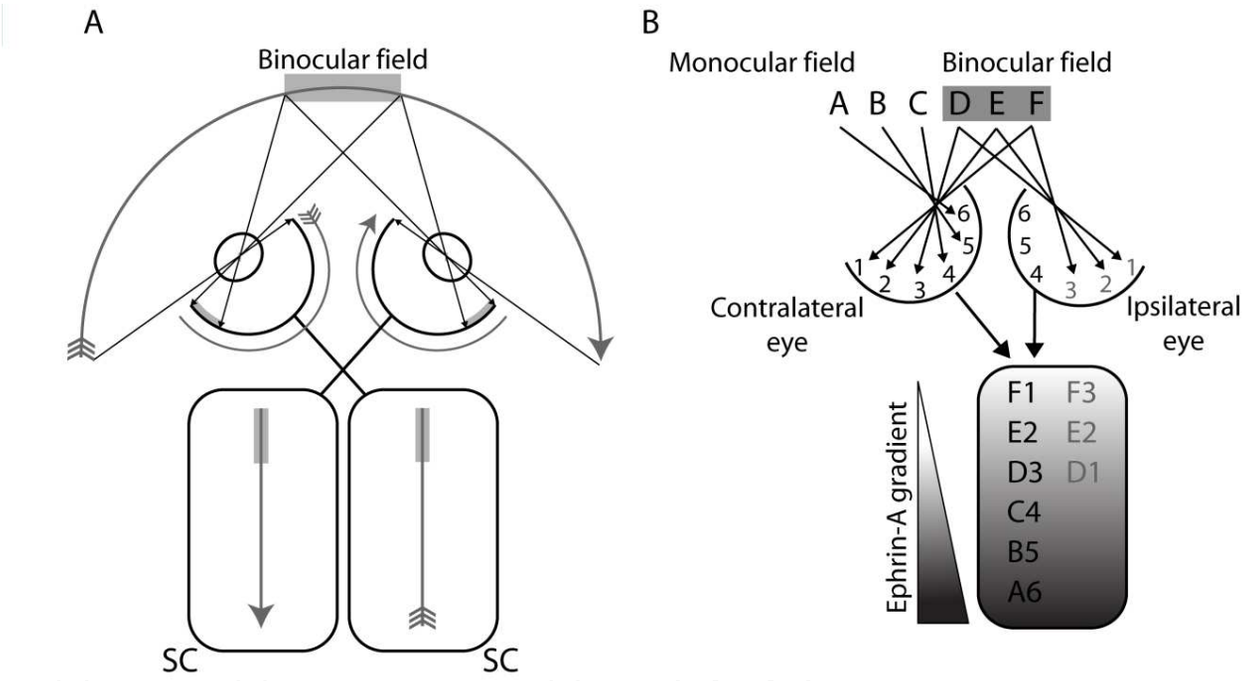


Figure 2. Monocular and binocular representation of the visual field in the superior colliculus (SC) in mice, modified from [2]. A: diagrammatic representation of visual field mapping across both SCs. B Diagrammatic representation of the integration of the ipsilateral and contralateral retinal projections within a single SC, and the resulting representation of visual field information. Letters represent visual field information and numbers represent RGCs within the retina and their terminations within the SC. In mice, the ipsilateral and contralateral retinal axons (numbers) project in reverse orientation relative to each other within the SC, providing a continuous representation of the binocular visual field (letters).

The reversal of the orientation of the ipsilateral relative to the contralateral map is also observed in the dLGN as illustrated by the Siamese cat experiments (see below). This organisation raises several possibilities of the mechanisms underpinning the organisation of the ipsilateral projection. One possibility is that unique guidance cues that are specific to the uncrossed projection might be expressed on RGC axons or within the SC. Alternatively, the same molecular cues might differentially guide ipsilateral and contralateral RGCs. A third possibil-

http://dx.doi.org/10.5772/56491

ity is that the ipsilateral projection maps onto the contralateral projection by activity-dependent mechanisms based on the similarity of visual information from both eyes. We will describe the development of both structures (SC and dLGN) and for each, review experiments that address the possible mechanisms of integration of ipsilateral and contralateral projections.

6. Development of the contralateral and ipsilateral retinal projections in mice

Retinal ganglion cells are generated between embryonic (E) days 11-19 in pigmented mice [23]. Contralaterally and ipsilaterally projecting RGCs are generated at the same time, though not on the same timetable; cells which cross at the optic chiasm are generated throughout this period, whereas cells that do not cross are generated within ventro-temporal retina mostly between E11-E16 [23]. Murine RGC axons reach the optic chiasm by E14 [24] where they make the decision to cross (contralateral RGCs) or not (ipsilateral RGCs; [25]).

6.1. Development of the superior colliculus in mice

The superior colliculus of the midbrain has an important role in integrating cortical and retinal inputs, and functionally is involved in recognition, localization and responsiveness to novel stimuli (Sefton et al., 2004). The majority of visually driven input to the superficial layers of the SC is from the retina and the primary visual cortex and, as for the dLGN, mapping of the ipsilateral and contralateral visual projections provides a continuous representation of the visual field even though the inputs are anatomically segregated. There are also auditory and somatosensory inputs to intermediate and deep SC layers as well as input from secondary visual cortices, parabigeminal nucleus, and a large number of nuclei in the brainstem [26,27]. Major outputs are to the thalamus, the pons, as well as brainstem nuclei and spinal cord segments involved in the control of head and neck movements [10,26,27,28,29].

There are seven layers in the superior colliculus in mammals. The most superficial three layers primarily receive retinal input: the *stratum zonale, stratum griseum superficiale* and the *stratum opticum* [26,30,31]. The superficial layers receive also inputs from the visual cortex and the intermediate and deep layers receive input from other cortical areas [32].

The neurons of the SC in the mouse are produced between E11-E13, with the most superficial layers being produced last [33]. Layers resembling those seen in the mature mouse are present by postnatal (P) day 6 [33,34]. Contralateral RGC axonal outgrowth is present in the SC by E15 and continues after birth [24,33,34,35]. Ipsilateral fibres appear later, around E19 until P3 [24]. Incoming contralateral [36] and ipsilateral [37] axons all extend past their appropriate termination zones and as a result, input is initially scattered and widespread [38], with only rough retinotopic topography and without segregation of ipsilateral and contralateral fibres. Refinement of the projections (topography and eye-specific) occurs by the formation along the rostrocaudal axis of interstitial branches that are targeted to the location of the topographically appropriate termination zone [39]. There is evidence for the interaction between TrkB/BDNF

and ephrin-A ligands to promote topographic specific branching [40]. These branches form dense arborisations within the superficial grey layer of the SC and any ectopic branches and overshooting axons are removed [41,42,43,44]. Pruning begins to occur by P4 and is complete by P8-P11 for both contralateral and ipsilateral projections [24,37]. As a result, the retinocollicular map is established and refined in the first two postnatal weeks [45] such that temporal retinal axons project to rostral SC and nasal retinal axons project to caudal SC. The ipsilateral axons terminate in small patches that are within the rostro-medial superficial grey but located slightly deeper than the contralaterally projecting axons [10].

6.2. Development of the LGN and visual cortex

In the mouse, contralateral RGC axons arrive in the dLGN by E16 and ipsilateral axons by E18 [24]. Mature retinotopy in the dLGN is mapped such that temporal axons project to dorsomedial dLGN and nasal axons project to ventrolateral dLGN. There is overlap of contralateral and ipsilateral fibres during the first postnatal week; segregation occurs before the eyes open and is complete by the end of the second postnatal week (P12-14) [41,46] with the ipsilateral terminals being restricted to an isolated roughly trapezoid shape patch within the contralateral terminals [47,48]. Carnivorous mammals such as cats, ferrets and shrews, as well as primates, have more complex layering and segregation within the dLGN based on the characteristics of the RGC inputs [49], reflecting their more sophisticated thalamo-cortical visual processing circuitries.

From the LGN, information from both eyes is carried to neurons in layer 4 of primary visual cortex. In cats and primates [50,51], ipsilateral and contralateral inputs are segregated into ocular dominance columns in layer 4 throughout V1. By contrast in rodents, only lateral visual cortex receives binocular inputs with the medial part being purely monocular [52,53,54]. Nonetheless, in all mammals, ipsilateral and contralateral inputs converge on neurons in layer 2/3, where processing of binocular disparity and thus stereopsis occurs.

7. Visual maps — Molecular mechanisms of topography

The circuitry of the visual system is established via complex guidance mechanisms that involve responses to molecular cues, and interactions between projections by activity-dependent mechanisms [1,55,56]. During development, newly-generated neurons send out developing axons that are guided in their outgrowth via cues which may be diffusible or cell-surface bound, and which may attract or repulse actively growing processes [56]. These various molecular cues assist in targeting, axon fasciculation, and the pruning of inappropriate axonal arbours. Targeting is both structural (in assisting the axon to locate the correct structure within the brain) and detailed (so that the connections are to the correct postsynaptic cell in the appropriate cell layer). In addition, activity dependent pruning further refines the developing projections such that accuracy is maximised [57,58,59]. This review will focus on Eph/ephrin interactions and Teneurins since these proteins have been shown to be important in establishing topography within the ipsilateral as well as the contralateral projection [2,3]. Other

http://dx.doi.org/10.5772/56491

guidance cues for example semaphorins, engrailed and L1 are crucial for the contralateral projection [60,61,62] In addition other molecules that have been implicated in eye specific segregation and terminal arborisation, but not in fundamental topographic organisation of the ipsilateral projection, such as BDNF, nitric oxide and the NMDA receptor [63,64,65] will not be discussed further.

7.1. Ephrins and Teneurins guide topography within the ipsilateral projection

The property which makes ephrins and Teneurins unique and ideally suited to topographic mapping between brain regions is their graded expression patterns. This mechanism of action is consistent with the 'chemoaffinity hypothesis', first proposed by Sperry [66] some time before the molecules were identified. This theory predicted that topographic mapping would require unique cytochemical cues expressed by each RGC and its target neuron in the SC. Within the visual system, the Eph/ephrin and teneurin proteins fulfilled this prediction by their graded expression across the origin and target structures in interconnected regions (retina – SC ; retina – dLGN – visual cortex) [55], conferring a unique coordinate in each structure by amount of protein [3,67,68,69].

7.1.1. Ephs and Ephrins

Ephrins are cell-surface bound ligands that bind to Eph receptors, which are receptor tyrosine kinases. The Eph/ephrin interaction is involved in cell-contact mediated signalling that aids cell and tissue organisation [70,71] There are two classes of ephrin ligands, ephrin-A and ephrin-B, classified according to mechanisms of membrane attachment. The members of the ephrin-A class are linked to the membrane by a glycerophospholipid and the ephrin-B class ligands are transmembrane molecules [72]. There are multiple ephrins and Eph receptors in the two classes; with some exceptions [73], ephrin-As will only bind to EphA receptors though binding within each class is non-specific and ligands are able to bind to multiple receptors [70].

Ephs and ephrins are expressed during nervous system development by the target tissue and growth cones of the developing axon. Following Eph-ephrin binding, the growth cone can be attracted (primarily through EphB-ephrin-B signalling) or repulsed (EphA-ephrin-A signalling) directing axons into appropriate regions within brain structures and setting up tissue boundaries and internal organisation [74,75]. The mechanism of growth cone stabilisation or collapse is by modulation of the cytoskeleton [76,77] and can occur bidirectionally via the ephrin and/or the Eph receptor [78,79]. In addition, both receptors and ligands are found to be expressed in the tissue of origin and in the target cells, further regulating the signal transduction process and sensitivity to target guidance cues [80,81,82].

7.1.2. Eph/ephrins in mapping visual projections

During development retinal ganglion cells make a crucial choice at the chiasm. The partial decussation of retinal axons at the optic chiasm is thought to be due to the action of ephrin-B ligands, specifically ephrin-B2 [83] which is expressed on specialised radial glial cells that are situated each side of the midline at the base of the third ventricle [84]. This localised ephrin-

B1 at the chiasm causes repulsion of ipsilaterally projecting RGC axons which express EphB1 [85,86,87] and as a result they do not cross but remain on the same side of the brain. However, EphB triple knockout mice retain some ipsilaterally projecting axons, suggesting that other molecules, such as Nogo [88,89] may also play a role.

Within the LGN, ephrin ligands and Eph receptors are expressed as gradients correlating topographic organisation of the contralateral projection [41]. During postnatal development, there is a correlation between a peak of ephrin expression and the segregation of eye-specific input to the dLGN when expression becomes restricted to the contralateral eye input areas of the dLGN, but no evidence that Eph/ephrin interactions regulate mapping of the ipsilateral retinogeniculate projection [41]. Similarly in visual cortex, there is evidence for a role of Eph/ephrin interactions in establishing contralateral but not ipsilateral topography [41,58].

By contrast, there is strong evidence for a role of Eph/ephrin interactions in establishing ipsilateral topography in the SC. Graded expression of ephrin ligands was first demonstrated in the tectum of the chick [67,68] and knockout mice subsequently confirmed the key role of these proteins in mapping the contralateral visual projection [45,90]. More recently, a role for ephrins in mapping the ipsilateral projection in the superior colliculus was demonstrated by anatomical tracing and electrophysiological experiments which compared the distribution of ipsilateral and contralateral projections [2]. The ipsilateral projection was expanded to fill the full extent of the SC and the organisation of the projection was highly abnormal and misaligned with the contralateral one. Furthermore, the study showed a behavioural deficit that could be rescued by blocking the input to one eye, confirming that although small in size, the ipsilateral projection has significant functional impact [2].

7.1.3. Teneurins

In most species studied to date, the Teneurin family contains four members (Ten-m1-4; [91], which are large transmembrane proteins that are found as homo or heterodimers [92,93]. They are believed to interact with Ten-m molecules on other cells via homophilic or heterophilic interactions [92,94].

Like Ephs and ephrins, Teneurins are expressed as gradients within many regions of the developing brain [95] and relevant to this chapter, have matching gradients across the interconnected visual brain regions (retina, dLGN, SC and visual cortex; [3,96]. However, in contrast to the Ephs and ephrins, very little is known about how the Teneurins exert their guidance activity. In response to binding, Teneurins have several potential signalling methods involving the extracellular and intracellular domains. The C-terminus (extracellular domain) of Teneurins can be cleaved by furin to produce a peptide with homology to the corticotrophin releasing factor (CRF; [97,98]) that has been shown to influence neurite extension and anxiety-related behaviours [99,100]. In addition, the intracellular domain has multiple tyrosine phosphorylation sites, calcium binding motifs and two SH3 binding sites, providing opportunities to interact with many signalling pathways as well as the cytoskeleton [101]. Furthermore, the intracellular domain has been shown to translocate to the nucleus and regulate transcription [101,102].

7.1.4. Ten_m3 in mapping visual projections

One of the Teneurin family members, Ten_m3, has been shown to play a key role in the organisation of eye specific inputs in the dLGN and visual cortex [3,103] and similar to the ephrins, is expressed in matching gradients across the retina and visual brain regions [3]. However, unlike Eph/ephrin interactions, Ten_m3 appears to have no impact on the contralateral projection. Expression peaks during early postnatal development and is highest in regions of the visual pathway associated with the ipsilateral projection. The role of Ten_m3 in mapping the ipsilateral projection was demonstrated in Ten_m3 knockout mice, in which normal numbers of ipsilaterally projecting RGCs are present, but their terminals extend abnormally broadly within the dLGN, covering the full dorso-medial to ventrolateral extent of the nucleus and invading regions that are normally monocular (contralateral) [3]. Normal segregation of the eye-specific inputs in these mice combined with normal contralateral topography further confirmed a specific effect of Ten_m3 on topographic mapping of ipsilateral projections. Aberrant projections were also observed in visual cortex, where ipsilateral input was not restricted to the laterally located binocular zone, but rather formed patches within the monocular region that are reminiscent of ocular dominance domains [103]. Furthermore, recording from cortical cells confirmed that binocular stimulation leads to functional suppression of mismatched binocular inputs [103]. Similar to results with ephrin-A knockout mice, Ten_m3 have abnormal visual function that can be rescued by blocking the input from one eye by injecting tetrodotoxin [3]. Ten_m3 is also implicated in mapping the ipsilateral projection within the SC [37] with knockout mice displaying mapping errors in both horizontal and azimuthal axes of the representation of the visual field. This study also examined for the first time the developmental time-course of ipsilateral retinocollicular projections relative to contralateral ones.

7.2. Research methodologies/tools

For the Ephs and ephrins, an important tool used to study this graded expression pattern was the stripe assay, which studied the growth behaviours of RGCs from different retinal locations on substrates made up of collicular membranes [104,105]. Temporal axons were more inhibited than nasal axons, and though they would grow on both anterior and posterior collicular membranes, they showed a preference for anterior membranes, their natural target [106]. Nasal axons did not show a consistent preference (although see [107]). Perhaps surprisingly, Ten-ms have not been studied in the stripe assay, possibly because the technique has not been used in recent years: although membrane stripe assays provided a foundation for understanding how the retinotopic map develops, there are limitations with these studies. The artificial *in vitr*o conditions, sometimes using lysed or non-neuronal cells, did not reproduce the complex environment of the developing brain and may have adversely affected retinal explant outgrowth. These initial studies also failed to identify the importance of the concentration gradient itself [69,108,109] or the complexity of the multiple interactions between ephrins and other proteins that have since been elucidated [43,110,111]. However, such studies provided the useful background for studying topographical development *in vivo*. A particular limitation has been in the study of ipsilaterally projecting RGCs which represent such a small proportion

of the total RGCs that their behaviour, even if different from that of contralaterally projecting cells, would not have been noted.

For both molecules, transgenic mice have been key tools in elucidating their role in guiding visual projections, in particular single, double and triple ephrin-A knockout mice [45,112,113], as well as Ten_m3 knockout mice [3,37], which provide much of the data reviewed below. Other Eph transgenic mice have been useful in elucidating the principles of topographic mapping by Ephs, in particular an elegant study by Brown and colleagues which demonstrates the importance of graded expression in point to point mapping [69].

8. Mechanisms of ipsilateral mapping in the superior colliculus: enucleation model

As reviewed above, the development of the ipsilateral retinocollicular projection is at least in part regulated by molecular guidance cues. However, studies that removed one eye at birth have indicated that the contralateral projection has an influence on the development of the ipsilateral projection. In monocular enucleation, one eye is removed at, or in some cases, before birth [114,115]. The age of enucleation has a significant effect on the surviving ipsilateral pathway. Rats enucleated at birth have an expanded uncrossed retinofugal pathway whereas those enucleated prenatally (E16.5) develop a smaller pathway than normal [114]; there is a greater number of retinal ganglion cells which project ipsilaterally and this seems to be due to an increase in survival of those retinal ganglion cells which would die under normal conditions [7]. A similar effect is seen in pigmented mice enucleated *in utero* [5,116] as well as in other species when prenatal and neonatal enucleation time-points are compared [117]. It seems that the two events which affect this outcome are whether the fibres have reached the chiasm and terminal location at enucleation [114].

The main change in the surviving ipsilateral RGC pathway is in the failure of retraction of growth into more caudally located regions of the superior colliculus that are normally occupied by terminations from the contralateral eye. In rats enucleated on at birth and then examined as adults, functional terminations were recorded in locations more caudal relative to their retinal position than seen in the ipsilateral projections of normal rats [5]. Crucially, the topography of this projection is as per the normal (non-enucleated) ipsilateral pattern. A similar result was obtained in the dLGN following enucleation in rats [118]. However, when rats were enucleated before birth, there was a reversal in the polarity of rostral-caudal mapping in the SC [5]. This suggests the importance of prior innervation of contralateral axons to the SC in the final distribution of ipsilateral terminations as contralateral RGC axons enter the SC prior to birth, whereas the ipsilateral axons arrive later [24].

The finding of normal ipsilateral topography in the SC following monocular enucleation at birth is particularly interesting when considered in the context of how RGC axons respond to the ephrin gradient. Typically, temporal RGC axons terminate in the contralateral rostral superior colliculus. However, those that project ipsilaterally terminate in more caudal positions, suggesting they either ignore or respond differently to the repulsive ephrin gradient

that restricts contralateral temporal axons to rostral SC (Figure 2). Moreover, the results highlight that ipsilateral RGC axons can terminate in topographically appropriate locations even in the absence of the contralateral retinocollicular topographic map.

9. Mechanisms of ipsilateral mapping in dLGN and V1: Siamese cats

A key model that has provided insight into the organisation of the ipsilateral projection in the LGN and visual cortex is the Siamese cat. As described by several groups, the visual system of the Siamese cat has a reduced ipsilateral retinal projection, resulting in significant reorganisation within the dLGN and visual cortex [119,120,121]. The abnormality has been definitively linked to a homozygous mutation at the albino locus[122] which affects chiasm crossing by RGC axons [123]. Interestingly, at least in the cat, the extent of ipsilateral and contralateral projections is different for different RGC subtypes [124,125]. It remains unclear to this day how changes in pigmentation affect this specific aspect of axonal guidance [126].

In Siamese cats, retinogeniculate fibers representing about the first 20 degrees of ipsilateral visual field in each eye cross aberrantly in the optic chiasm, providing a larger retinal input to the contralateral dLGN [119]. There is not sufficient space for these aberrant fibres to terminate in the A lamina of the dLGN where contralateral fibres would normally arrive. Therefore they overflow into the A1 lamina of the dLGN that normally receives ipsilateral input [119,127]. Furthermore, anatomical and physiological studies of the LGN confirm that this additional projection aligns itself with the topography of the ipsilateral but not contralateral projections, resulting in a "mirror image" of the normal representation [119].

The organisation of ipsilateral projections within the dLGN is thus severely disordered and predictably results in downstream rearrangement of visual pathways in the geniculocortical [121,128], corticogeniculate [129,130] and callosal projections [131,132], as well as cortical associational pathways [130]. Interestingly, when an albino-like representation of the ipsilateral hemifield is induced in the visual cortex of normally pigmented cats, these downstream defects are also observed, suggesting that they are secondary to the initial misrouting of ganglion cells at the optic chiasm [133] rather than a direct consequence of the albino mutation [134].

Most attention has been focused on the geniculocortical pathway, where previous work has reported two distinct modes of processing the aberrant retinal input to the LGN [135]. Work carried out at Harvard defined the "Boston" variety of Siamese cat [121], in which the input that arises from the abnormal section of the dLGN is modified to integrate into cortical map and provide a continuous topographic representation of the visual field. By contrast, work in a Chicago laboratory defined the "Midwestern" Siamese cat [128], in which the abnormal input from the dLGN is silenced. Importantly, these two models provided an opportunity to examine the behavioural consequences of abnormal binocular inputs to LGN and visual cortex. In agreement with the low numbers of binocularly driven cells in visual cortex [136], stereoscopic depth perception and binocular summation in contrast sensitivity have been found to be impaired in Siamese cats [137,138]. However, there was no correlation between squint and the

extent of ipsilateral visual field represented in the visual cortex for either variety of Siamese cat [127].

10. Implications for human pathologies

The importance of binocular integration in the visual centres is evidenced by the loss of visual acuity that can occur in amblyopic individuals. Amblyopia is a broad pathological condition where there is dysfunction in the processing of visual information [139]. It can be caused by misalignment of the retinal output to the brain, in disorders such as strabismus (ocular misalignment, such as in 'lazy eye' syndromes), anisometropia (differences in refractive error), and monocular deprivation [139]. The downstream effects of such pathologies involve a degradation of visual acuity and other visual functions associated with binocular processing due to misalignment of retinal inputs.

A more complete loss of visual function occurs with monocular enucleation in which one eye is removed, and provides a unique opportunity to study the importance of binocularity in humans. In such cases, both motion processing and oculomotor behaviour are reduced in enucleated individuals [140]. This processing occurs in the associative visual cortex areas and in the midbrain and suggests the importance of binocular summation in these tasks. However, in some tests related to spatial acuity, enucleated individuals performed better than normally sighted people, although this was strongly related to the age at which enucleation occurred. This may be due to the adaptable nature of the cortex, with incoming connections from the intact eye taking up a relatively larger area of the cortex.

Although rodents are often used as models for the study of the visual system, the crossover at the optic chiasm (3%) is considerably less than that of humans (50%). However, the treatment paradigms which have been studied in rodents may still be applicable to humans due to the similarities in the plastic nature of the visual cortex. The visual cortex is especially sensitive to external influences such as amblyopic pathologies during the critical period. This can last up to 7 years in humans, but only 5 weeks in mice (~32 days [141]; rats [142]). During this time, if there are any abnormalities, they can be successfully treated by intervention because the neuronal connections are still developing. The task becomes considerably harder once the critical period has closed, but work in rodents can help to study treatments which may work in older individuals in recovering visual acuity.

Loss of visual acuity can be induced in a rodent model of through the use of monocular deprivation, in which one eyelid is sutured during the critical period of postnatal development and the remaining eye then becomes dominant in the visual cortex, a phenomenon first described in cats [143]. Typically, such a condition can be reversed if the deprivation effects are terminated during the critical period [144,145,146,147] and, though it is possible, there is less chance of recovery if not treated until adulthood [148]. In addition to pharmacological interventions, which at present lack clinical feasibility [149], a promising experimental treatment recently described in the rodent model involves environmental enrichment, which

has been shown to rescue the visual acuity of amblyopic rats in adulthood if there is damage to one eye [150].

11. Conclusion

Binocular vision requires integration of the inputs from both eyes onto neurons in the major visual brain centres. There is a challenge to understanding how these distinct inputs map the binocular field because the ipsilateral projection maps in the opposite direction relative the contralateral one. Most of the known cues which guide the development of visual mapping in the brain relate to the contralateral eye only, with little known about ipsilateral mapping. Animal models, especially in cat and rodents, have been used to study both normal and abnormal integration of the two eyes and to elucidate the mechanisms underpinning this process. There is also the capacity for further work in animal models, especially with regard to possible interventions for disorders of binocular integration such as amblyopia.

Acknowledgements

We are grateful to Marissa Penrose for figure production. JR is a National Health and Medical Research Council Australia Senior Research Fellow.

Author details

Tenelle A. Wilks, Alan R. Harvey and Jennifer Rodger

Schools of Animal Biology and Anatomy, Physiology and Human Biology, The University of Western Australia, Crawley WA, Australia

References

[1] McLaughlin T, O'Leary DD. Molecular gradients and development of retinotopic maps. Annu Rev Neurosci 2005; 28 327-355.

[2] Haustead D, Lukehurst S, Clutton GB, Dunlop S, Arrese CA, Sherrard RM, Rodger J. Functional topography and integration of the contralateral and ipsilateral retinocollicular projections in ephrin-A-/- mice. J Neurosci 2008; 28 (29): 7376-7386.

[3] Leamey CA, Merlin S, Lattouf P, Sawatari A, Zhou X, Demel N, Glendining KA, Oohasi T, Sur M, Fassler R. Ten_m3 regulates eye-specific patterning in the mammalian

visual pathway and is required for binocular vision. PLoS Biology 2007; 5 (9): 2077-2092.

[4] Bishop PO, Pettigrew JD. Neural mechanisms of binocular vision. Vision Res 1986; 26 (9): 1587-1600.

[5] Jeffery G, Thompson ID. The effects of prenatal and neonatal monocular enucleation on visual topography in the uncrossed retinal pathway to the rat superior colliculus. Exp Brain Res 1986; 63 (2): 351-363.

[6] Drager UC, Olsen JF. Origins of crossed and uncrossed retinal projections in pigmented and albino mice. J Comp Neurol 1980; 191 (3): 383-412.

[7] Jeffery G. Retinal ganglion cell death and terminal field retraction in the developing rodent visual system. Brain Res 1984; 315 (1): 81-96.

[8] Heesy C. On the relationship between orbit orientation and binocular visual field overlap in mammals. Anat Record 2004; 281A 1104-1110.

[9] Balkema GW, Pinto LH, Drager UC, Vanable JW. Characterisation of abnormalities in the visual system of the mutant mouse pearl. J Neurosci 1981; 1 (11): 1320-1329.

[10] Sefton AJ, Dreher B, Harvey AR (2004) Visual System. In: Paxinos G, editor. The Rat Nervous System. 3rd ed. San Diego: Elsevier Academic Press. pp. 1083-1165.

[11] Hughes A (1977) The topography of vision in mammals. In: Crescitelli C, editor. Handbook of Sensory Physiology. Heidelberg: Springer Verlag. pp. 615-756.

[12] Illing RB, Wassle H. The retinal projection to the thalamus in the cat: a quantitative investigation and a comparison with the retinotectal pathway. J Comp Neurol 1981; 202 (2): 265-285.

[13] Stone J, Campion JE, Leicester J. The nasotemporal division of retina in the Siamese cat. J Comp Neurol 1978; 180 (4): 783-798.

[14] Morland AB, Hoffmann MB, Neveu M, Holder GE. Abnormal visual projection in a human albino studied with functional magnetic resonance imaging and visual evoked potentials. J Neurol Neurosurg Psychiatry 2002; 72 (4): 523-526.

[15] Cumming BG, DeAngelis GC. The physiology of stereopsis. Annu Rev Neurosci 2001; 24 203-238.

[16] Wheatstone C. Contributions to the physiology of vision.-Part the First. On some remarkable, and hitherto unobserved, phænomena of binocular vision. Philosophical Transactions of the Royal Society of London 1838; 128 371–394.

[17] Ponce CR, Born RT. Stereopsis. Curr Biol 2008; 18 (18): R845-850.

[18] Panum P Physiologische Untersuchungen über das Sehen mit zwei Augen. 1858. Kiel: Schwerssche Buchhandlung.

[19] Gonzalez F, Perez R. Neural mechanisms underlying stereoscopic vision. Prog Neurobiol 1998; 55 (3): 191-224.

[20] McLaughlin T, Hindges T, O'Leary DDM. Regulation of axial patterning of the retina and its topographic mapping in the brain. Curr Op Neurobiol 2003; 13 57-69.

[21] Leamey CA, Wart AV, Sur M. Intrinsic patterning and experience-dependent mechanisms that generate eye-specific projections and binocular circuits in the visual pathway. Current Opinion in Neurobiology 2009; 19 (2): 181-187.

[22] Lambot MA, Depasse F, Noel JC, Vanderhaeghen P. Mapping labels in the human developing visual system and the evolution of binocular vision. J Neurosci 2005; 25 (31): 7232-7237.

[23] Drager U. Birth dates of retinal ganglion cells giving rise to the crossed and uncrossed optic projections in the mouse. Proc R Soc Lond B Biol Sci 1985; 224 57-77.

[24] Godement P, Salaun J, Imbert M. Prenatal and postnatal development of retinogeniculate and retinocollicular projections in the mouse. J Comp Neurol 1984; 230 (4): 552-575.

[25] Jeffery G. Architecture of the optic chiasm and the mechanisms that sculpt its development. Physiological Reviews 2001; 81 (4): 1393-1414.

[26] Drager UC, Hubel DH. Responses to visual stimulation and relationship between visual, auditory, and somatosensory inputs in mouse superior colliculus. Journal of Neurophysiology 1975; 28 (3): 690.

[27] Drager UC, Hubel DH. Topography of visual and somatosensory projections to mouse superior colliculus. J Neurophysiol 1976; 39 (1): 91-101.

[28] Westby GWM, Keay KA, Redgrave P, Dean P, Bannister M. Output pathways from the rat superior colliculus mediating approach and avoidance have different sensory properties. Experimental Brain Research 1990; 81 (3): 626-638.

[29] Mooney RD, Nikoletseas MM, Hess PR, Allen Z, Lewin AC, Rhoades RW. The projection from the superficial to the deep layers of the superior colliculus: An intracellular horseradish peroxidase injection study in the hamster. The Journal of Neuroscience 1998; 8 (4): 1384-1399.

[30] Chalupa LM, Williams RW, editors (2008) Eye, retina and visual system of the mouse. Cambridge, Massachusetts: MIT Press.

[31] Stein BE. Development of the superior colliculus. Annual Review of Neuroscience 1984; 7 95-125.

[32] Lund RD. The occipitotectal pathway of the rat. J Anat 1966; 100 (Pt 1): 51-62.

[33] Edwards MA, Caviness Jr. VS, Schneider GE. Development of cell and fiber lamination in the mouse superior colliculus. Journal of Comparative Neurology 1986; 248 (248): 395-409.

[34] Edwards MA, Schneider GE, Caviness Jr. VS. Development of the crossed retinocollicular projection in the mouse. Journal of Comparative Neurology 1986; 248 (3): 410-421.

[35] Dallimore EJ, Park KK, Pollett MA, Taylor JS, Harvey AR. The life, death and regenerative ability of immature and mature rat retinal ganglion cells are influenced by their birthdate. Exp Neurol 2010; 225 (2): 353-365.

[36] Simon DK, O'Leary DD. Development of topographic order in the mammalian retinocollicular projection. J Neurosci 1992; 12 (4): 1212-1232.

[37] Dharmaratne N, Glendining KA, Young TR, Tran H, Sawatari A, Leamey CA. Ten-m3 Is Required for the Development of Topography in the Ipsilateral Retinocollicular Pathway. PLoS ONE 2012; 7 (9): e43083.

[38] Lund RD, Bunt AH. Prenatal development of central optic pathways in albino rats. J Comp Neurol 1976; 165 (2): 247-264.

[39] Yates PA, Roskies AL, McLaughlin T, O'Leary DDM. Topographic-specific axon branching controlled by ephrin-As is the critical event in retinotectal map development. Journal of Neuroscience 2001; 21 (21): 8548–8563.

[40] Marler KJ, Becker-Barroso E, Martinez A, Llovera M, Wentzel C, Poopalasundaram S, Hindges R, Soriano E, Comella J, Drescher U. A TrkB/EphrinA interaction controls retinal axon branching and synaptogenesis. J Neurosci 2008; 28 (48): 12700-12712.

[41] Pfeiffenberger C, Cutforth T, Woods G, Yamada J, Renteria RC, Copenhagen DR, Flanagan JG, Feldheim DA. Ephrin-As and neural activity are required for eye-specific patterning during retinogeniculate mapping. Nature Neuroscience 2005; 8 (8): 1022-1027.

[42] Huberman AD. Mechanisms of eye-specific visual circuit development. Current Opinion in Neurobiology 2007; 17 (1): 73-80.

[43] Nicol X, Muzerelle A, Rio J, Metin C, Gaspar P. Requirement of Adenylate Cyclase 1 for the ephrin-A5-dependent retraction of exuberant retinal axons. J Neurosci 2006; 26 (3): 862-872.

[44] Nicol X, Voyatzis S, Muzerelle A, Narboux-Neme N, Sudhof T, Miles R, Gaspar P. cAMP oscillations and retinal activity are permissive for ephrin signalling during the establishment of the retinotopic map. Nat Neurosci 2007; 10 (3): 340-347.

[45] Frisen J, Yates PA, McLaughlin T, Friedman GC, O'Leary DD, Barbacid M. Ephrin-A5 (AL-1/RAGS) is essential for proper retinal axon guidance and topographic mapping in the mammalian visual system. Neuron 1998; 20 (2): 235-243.

[46] Jaubert-Miazza L, Green E, Lo F-S, Bui K, Mills J, Guido W. Structural and functional composition of the developing retinogeniculate pathway in the mouse. Visual Neuroscience 2005; 22 (5): 661-676.

[47] Lund RD, Lund J, S., Wise RP. The organization of the retinal projection to the dorsal lateral geniculate nucleus in pigmented and albino rats. Journal of Comparative Neurology 1974; 158 (4): 383-404.

[48] Godement P, Saillour P, Imbert M. The ipsilateral optic pathway to the dorsal lateral geniculate nucleus and superior colliculus in mice with prenatal or postnatal loss of one eye. Journal of Comparative Neurology 1980; 190 (4): 611-626.

[49] Sillito AM, Jones HE. Corticothalamic interactions in the transfer of visual information. Philosophical Transactions: Biological Sciences 2002; 357 (1428): 1739-1752.

[50] Hubel DH, Wiesel TN. Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. J Physiol 1962; 160 (1): 106-154.

[51] Gattass R, Nascimento-Silva S, Soares JG, Lima B, Jansen AK, Diogo AC, Farias MF, Botelho MM, Mariani OS, Azzi J, Fiorani M. Cortical visual areas in monkeys: location, topography, connections, columns, plasticity and cortical dynamics. Philos Trans R Soc Lond B Biol Sci 2005; 360 (1456): 709-731.

[52] Adams AD, Forrester JM. The projection of the rat's visual field on the cerebral cortex. Q J Exp Physiol Cogn Med Sci 1968; 53 (3): 327-336.

[53] Montero VM. Evoked responses in the rat's visual cortex to contralateral, ipsilateral and restricted photic stimulation. Brain Res 1973; 53 (1): 192-196.

[54] Thurlow GA, Cooper RM. Metabolic activity in striate and extrastriate cortex in the hooded rat: contralateral and ipsilateral eye input. J Comp Neurol 1988; 274 (4): 595-607.

[55] Goodhill G, Richards L. Retinotectal maps: molecules, models and misplaced data. Trends in Neuroscience 1999; 22 (12): 529-534.

[56] Feldheim DA, O'Leary DD. Visual map development: bidirectional signaling, bifunctional guidance molecules, and competition. Cold Spring Harb Perspect Biol 2010; 2 (11): a001768.

[57] McLaughlin T, Hindges R, O'Leary DDM. Regulation of axial patterning of the retina and its topographic mapping in the brain. Current Opinion in Neurobiology 2003; 13 (1): 57-69.

[58] Cang J, Kaneko M, Yamada J, Woods G, Stryker MP, Feldheim DA. Ephrin-As guide the formation of functional maps in the visual cortex. Neuron 2005; 48 (4): 577-589.

[59] Mrsic-Flogel TD, Hofer SB, Creutzfeldt C, Cloez-Tayarani I, Changeux J-P, Bonhoeffer T, Hubener M. Altered map of visual space in the superior colliculus of mice lacking early retinal waves. The Journal of Neuroscience 2005; 25 (29): 6921- 6928.

[60] Claudepierre T, Koncina E, Pfrieger FW, Bagnard D, Aunis D, Reber M. Implication of neuropilin 2/semaphorin 3F in retinocollicular map formation. Dev Dyn 2008; 237 (11): 3394-3403.

[61] Wizenmann A, Brunet I, Lam JS, Sonnier L, Beurdeley M, Zarbalis K, Weisenhorn-Vogt D, Weinl C, Dwivedy A, Joliot A, Wurst W, Holt C, Prochiantz A. Extracellular Engrailed participates in the topographic guidance of retinal axons in vivo. Neuron 2009; 64 (3): 355-366.

[62] Demyanenko GP, Maness PF. The L1 cell adhesion molecule is essential for topographic mapping of retinal axons. J Neurosci 2003; 23 (2): 530-538.

[63] Rodger J, Frost DO. Effects of trkB knockout on topography and ocular segregation of uncrossed retinal projections. Exp Brain Res 2009; 195 (1): 35-44.

[64] Ernst AF, Wu HH, El-Fakahany EE, McLoon SC. NMDA receptor-mediated refinement of a transient retinotectal projection during development requires nitric oxide. J Neurosci 1999; 19 (1): 229-235.

[65] Mize RR, Wu HH, Cork RJ, Scheiner CA. The role of nitric oxide in development of the patch-cluster system and retinocollicular pathways in the rodent superior colliculus. Prog Brain Res 1998; 118 133-152.

[66] Sperry R. Chemoaffinity in the orderly growth of nerve fiber patterns and connections. Proc Natl Acad Sci USA 1963; 50 703-710.

[67] Cheng H-J, Flanagan J. Identification and cloning of ELF-1, a developmentally expressed ligand for the Mek4 and Sek receptor tyrosine kinases. Cell 1994; 79 (1): 157-168.

[68] Cheng H-J, Nakamoto M, Bergemann A, Flanagan J. Complementary gradients in expression and binding of ELF-1 and Mek4 in development of the topographic retinotectal projection map. Cell 1995; 82 (3): 371-381.

[69] Brown A, Yates PA, Burrola P, Ortuño D, Vaidya A, Jessell TM, Pfaff SL, OLeary DDM, Lemke G. Topographic mapping from the retina to the midbrain Is controlled by relative but not absolute levels of EphA receptor signaling. Cell 2000; 102 (1): 77-88.

[70] Wilkinson DG. Multiple roles of Eph receptors and ephrins in neural development. Nat Rev Neurosci 2001; 2 (3): 155-164.

[71] Triplett JW, Feldheim DA. Eph and ephrin signaling in the formation of topographic maps. Seminars in Cell & Developmental Biology 2012; 23 (1): 7-15.

[72] Pasquale EB. The Eph family of receptors. Current Opinion in Cell Biology 1997; 9 (5): 608-615.

[73] Himanen JP, Chumley MJ, Lackmann M, Li C, Barton WA, Jeffrey PD, Vearing C, Geleick D, Feldheim DA, Boyd AW, Henkemeyer M, Nikolov DB. Repelling class

discrimination: ephrin-A5 binds to and activates EphB2 receptor signaling. Nat Neurosci 2004; 7 (5): 501-509.

[74] Rodger J, Salvatore L, Migani P. Should I stay or should I go? Ephs and ephrins in neuronal migration. Neurosignals 2012; 20 (3): 190-201.

[75] North HA, Clifford MA, Donoghue MJ. 'Til Eph Do Us Part': Intercellular signaling via eph receptors and ephrin ligands guides cerebral cortical development from birth through maturation. Cerebral Cortex 2012.

[76] Davenport R, Thies E, Cohen M. Neuronal growth cone collapse triggers lateral extensions along trailing axons. Nature Neuroscience 1999; 2 254-259.

[77] Sahin M, Greer PL, Lin MZ, Poucher H, Eberhart J, Schmidt S, Wright TM, Shamah SM, O'Connell S, Cowan CW, Hu L, Goldberg JL, Debant A, Corfas G, Krull CE, Greenberg ME. Eph-dependent tyrosine phosphorylation of ephexin1 modulates growth cone collapse. Neuron 2005; 46 (2): 191-204.

[78] Davy A, Gale NW, Murray EW, Klinghoffer RA, Soriano P, Feuerstein C, Robbins SM. Compartmentalised signaling by GPI-anchored eprhin-A5 requires the Fyn tyrosine kinase to regulate cellular adhesion. Genes and Development 1999; 13 (23): 3125-3135.

[79] Davy A, Soriano P. Ephrin signaling in vivo: look both ways. Dev Dyn 2005; 232 (1): 1-10.

[80] Hornberger MR, Dutting D, Ciossek T, Yamada T, Handwerker C, Lang S, Weth F, Huf J, Weßel R, Logan C, Tanaka H, Drescher U. Modulation of EphA receptor function by coexpressed ephrinA ligands on retinal ganglion cell axons. Neuron 1999; 22 (4): 731-742.

[81] Marquardt T, Shirasaki R, Ghosh S, Andrews SE, Carter N, Hunter T, Pfaff SL. Coexpressed EphA receptors and ephrin-A ligands mediate opposing actions on growth cone navigation from distinct membrane domains. Cell 2005; 121 (1): 127-139.

[82] Carvalho RF, Beutler M, Marler KJM, Knoll B, Becker-Barroso E, Heintzmann R, Ng T, Drescher U. Silencing of EphA3 through a cis interaction with ephrin A5. Nature Neuroscience 2005; 9 (3): 322-330.

[83] Williams SE, Mason CA, Herrera E. The optic chiasm as a midline choice point. Current Opinion in Neurobiology 2004; 14 (1): 51-60.

[84] Marcus RC, Blazeski R, Godement P, Mason CA. Retinal axon divergence in the optic chiasm: uncrossed axons diverge from crossed axons within a midline glial specialization. J Neurosci 1995; 15 (5 Pt 2): 3716-3729.

[85] Nakagawa S, Brennan C, Johnson KG, Shewan D, Harris WA, Holt CE. Ephrin-B regulates the ipsilateral routing of retinal axons at the optic chiasm. Neuron 2000; 25 (3): 599-610.

[86] Williams SE, Mann F, Erskine L, Sakurai T, Wei S, Rossi DJ, Gale NW, Holt CE, Mason CA, Henkemeyer M. Ephrin-B2 and EphB1 mediate retinal axon divergence at the optic chiasm. Neuron 2003; 39 (6): 919-935.

[87] Petros TJ, Bryson JB, Mason C. Ephrin-B2 elicits differential growth cone collapse and axon retraction in retinal ganglion cells from distinct retinal regions. Dev Neurobiol 2010; 70 (11): 781-794.

[88] Wang J, Chan CK, Taylor JS, Chan SO. The growth-inhibitory protein Nogo is involved in midline routing of axons in the mouse optic chiasm. J Neurosci Res 2008; 86 (12): 2581-2590.

[89] Fabre PJ, Shimogori T, Charron F. Segregation of ipsilateral retinal ganglion cell axons at the optic chiasm requires the Shh receptor Boc. J Neurosci 2010; 30 (1): 266-275.

[90] Feldheim DA, Kim Y-I, Bergemann AD, Frisen J, Barbacid M, Flanagan JG. Genetic analysis of ephrin-A2 and ephrin-A5 shows their requirement in multiple aspects of retinocollicular mapping. Neuron 2000; 25 (3): 563-574.

[91] Tucker RP, Chiquet-Ehrismann R. Teneurins: a conserved family of transmembrane proteins involved in intercellular signaling during development. Dev Biol 2006; 290 (2): 237-245.

[92] Oohashi T, Zhou XH, Feng K, Richter B, Morgelin M, Perez MT, Su WD, Chiquet-Ehrismann R, Rauch U, Fassler R. Mouse ten-m/Odz is a new family of dimeric type II transmembrane proteins expressed in many tissues. J Cell Biol 1999; 145 (3): 563-577.

[93] Feng K, Zhou XH, Oohashi T, Morgelin M, Lustig A, Hirakawa S, Ninomiya Y, Engel J, Rauch U, Fassler R. All four members of the Ten-m/Odz family of transmembrane proteins form dimers. J Biol Chem 2002; 277 (29): 26128-26135.

[94] Rubin BP, Tucker RP, Brown-Luedi M, Martin D, Chiquet-Ehrismann R. Teneurin 2 is expressed by the neurons of the thalamofugal visual system in situ and promotes homophilic cell-cell adhesion in vitro. Development 2002; 129 (20): 4697-4705.

[95] Kenzelmann D, Chiquet-Ehrismann R, Leachman NT, Tucker RP. Teneurin-1 is expressed in interconnected regions of the developing brain and is processed in vivo. BMC Dev Biol 2008; 8 30.

[96] Leamey CA, Glendining KA, Kreiman G, Kang ND, Wang KH, Fassler R, Sawatari A, Tonegawa S, Sur M. Differential gene expression between sensory neocortical areas: potential roles for Ten_m3 and Bcl6 in patterning visual and somatosensory pathways. Cereb Cortex 2008; 18 (1): 53-66.

[97] Wang L, Rotzinger S, Al Chawaf A, Elias CF, Barsyte-Lovejoy D, Qian X, Wang NC, De Cristofaro A, Belsham D, Bittencourt JC, Vaccarino F, Lovejoy DA. Teneurin proteins possess a carboxy terminal sequence with neuromodulatory activity. Brain Res Mol Brain Res 2005; 133 (2): 253-265.

[98] Lovejoy DA, Rotzinger S, Barsyte-Lovejoy D. Evolution of complementary peptide systems: teneurin C-terminal-associated peptides and corticotropin-releasing factor superfamilies. Ann N Y Acad Sci 2009; 1163 215-220.

[99] Al Chawaf A, Xu K, Tan L, Vaccarino FJ, Lovejoy DA, Rotzinger S. Corticotropin-releasing factor (CRF)-induced behaviors are modulated by intravenous administration of teneurin C-terminal associated peptide-1 (TCAP-1). Peptides 2007; 28 (7): 1406-1415.

[100] Tan LA, Xu K, Vaccarino FJ, Lovejoy DA, Rotzinger S. Teneurin C-terminal associated peptide (TCAP)-1 attenuates corticotropin-releasing factor (CRF)-induced c-Fos expression in the limbic system and modulates anxiety behavior in male Wistar rats. Behav Brain Res 2009; 201 (1): 198-206.

[101] Nunes SM, Ferralli J, Choi K, Brown-Luedi M, Minet AD, Chiquet-Ehrismann R. The intracellular domain of teneurin-1 interacts with MBD1 and CAP/ponsin resulting in subcellular codistribution and translocation to the nuclear matrix. Exp Cell Res 2005; 305 (1): 122-132.

[102] Bagutti C, Forro G, Ferralli J, Rubin B, Chiquet-Ehrismann R. The intracellular domain of teneurin-2 has a nuclear function and represses zic-1-mediated transcription. J Cell Sci 2003; 116 (Pt 14): 2957-2966.

[103] Merlin S, Horng S, Marotte LR, Sur M, Sawatari A, Leamey CA. Deletion of Ten-m3 Induces the Formation of Eye Dominance Domains in Mouse Visual Cortex. Cereb Cortex 2012; Doi: 10.1093/cercor/bhs030.

[104] Baier H, Bonhoeffer F. Axon guidance by gradients of a target-derived component. Science 1992; 255 (5043): 472-475.

[105] Walter J, Kern-Veits B, Huf J, Stolze B, Bonhoeffer F. Recognition of position-specific properties of tectai cell membranes by retinal axons in vitro. Development 1987; 101 (4): 685-696.

[106] Walter J, Henke-Fahle S, Bonhoeffer F. Avoidance of posterior tectal membranes by temporal retinal axons. Development 1987; 101 (4): 909-913.

[107] von Boxberg Y, Deiss S, Schwarz U. Guidance and topographic stabilization of nasal chick retinal axons on target-derived components in vitro. Neuron 1993; 10 (3): 345-357.

[108] Hansen MJ, Dallal GE, Flanagan JG. Retinal axon response to ephrin-as shows a graded, concentration-dependent transition from growth promotion to inhibition. Neuron 2004; 42 (5): 717-730.

[109] Rosentreter SM, Davenport RW, Loschinger J, Huf J, Jung J, Bonhoeffer F. Response of retinal ganglion cell axons to striped linear gradients of repellent guidance molecules. J Neurobiol 1998; 37 (4): 541-562.

[110] Poopalasundaram S, Marler KJ, Drescher U. EphrinA6 on chick retinal axons is a key component for p75(NTR)-dependent axon repulsion and TrkB-dependent axon branching. Mol Cell Neurosci 2011; 47 (2): 131-136.

[111] Fitzgerald M, Buckley A, Lukehurst SS, Dunlop SA, Beazley LD, Rodger J. Neurite responses to ephrin-A5 modulated by BDNF: evidence for TrkB-EphA interactions. Biochem Biophys Res Commun 2008; 374 (4): 625-630.

[112] Feldheim D, Vanderhaeghen P, Hansen M, Frisen J, Lu Q, Barbacid M, Flanagan J. Topographic guidance labels in a sensory projection to the forebrain. Neuron 1998; 21 (6): 1303-1313.

[113] Cang J, Niell C, Liu X, Pfeiffenberger C, Feldheim D, Stryker M. Selective disruption of one cartesian axis of cortical maps and receptive fields by deficiency in ephrin-As and structured activity. Neuron 2008; 57 (4): 511-523.

[114] Chan SO, Guillery RW. Developmental changes produced in the retinofugal pathways of rats and ferrets by early monocular enucleations: the effects of age and the differences between normal and albino animals. J Neurosci 1993; 13 (12): 5277-5293.

[115] Land PW, Lund RD. Development of the rat's uncrossed retinotectal pathway and its relation to plasticity studies. Science 1979; 205 (4407): 698-700.

[116] Chan SO, Chung KY, Taylor JSH. The effects of early prenatal monocular enucleation on the routing of uncrossed retinofugal axons and the cellular environment at the chiasm of mouse embryos. European Journal of Neuroscience 1999; 11 (9): 3225-3235.

[117] Coleman L-A, Beazley LD. Retinal ganglion cell number is unchanged in the remaining eye following early unilateral eye removal in the wallaby Setonix brachyurus, quokka. Developmental Brain Research 1989; 48 (2): 293-307.

[118] Reese B. The topography of expanded uncrossed retinal projections following neonatal enucleation of one eye: differing effects in dorsal lateral geniculate nucleus and superior colliculus. J Comp Neurol 1986; 250 (1): 8-32.

[119] Guillery RW, Kaas JH. A study of normal and congenitally abnormal retinogeniculate projections in cats. J Comp Neurol 1971; 143 (1): 73-100.

[120] Kalil RE, Jhaveri SR, Richards W. Anomalous retinal pathways in the Siamese cat: an inadequate substrate for normal bioncular vision. Science 1971; 174 (4006): 302-305.

[121] Hubel DH, Wiesel TN. Aberrant visual projections in the Siamese cat. J Physiol 1971; 218 (1): 33-62.

[122] Creel DJ. Visual system anomaly associated with albinism in the cat. Nature 1971; 231 (5303): 465-466.

[123] Rice DS, Goldowitz D, Williams RW, Hamre K, Johnson PT, Tan SS, Reese BE. Extrinsic modulation of retinal ganglion cell projections: analysis of the albino mutation in pigmentation mosaic mice. Dev Biol 1999; 216 (1): 41-56.

[124] Kirk DL, Levick WR, Cleland BG. The crossed or uncrossed destination of axons of sluggish-concentric and non-concentric cat retinal ganglion cells, with an overall synthesis of the visual field representation. Vision Res 1976; 16 (3): 233-236.

[125] Kirk DL, Levick WR, Cleland BG, Wassle H. Crossed and uncrossed representation of the visual field by brisk-sustained and brisk-transient cat retinal ganglion cells. Vision Res 1976; 16 (3): 225-231.

[126] Guillery RW. Why do albinos and other hypopigmented mutants lack normal binocular vision, and what else is abnormal in their central visual pathways? Eye (Lond) 1996; 10 (Pt 2) 217-221.

[127] Shatz C. A comparison of visual pathways in Boston and Midwestern Siamese cats. J Comp Neurol 1977; 171 (2): 205-228.

[128] Kaas J, Guillery R. The transfer of abnormal visual field representations from lateral geniculate nucleus to the visual cortex in siamese cats. Brain Research 1973; 59 61-95.

[129] Montero VM, Guillery RW. Abnormalities of the cortico-geniculate pathway in Siamese cats. J Comp Neurol 1978; 179 (1): 1-12.

[130] Shatz CJ, LeVay S. Siamese cat: altered connections of visual cortex. Science 1979; 204 (4390): 328-330.

[131] Shatz C. Abnormal interhemispheric connections in the visual system of Boston Siamese cats: a physiological study. J Comp Neurol 1977; 171 (2): 229-245.

[132] Shatz CJ. Anatomy of interhemispheric connections in the visual system of Boston Siamese and ordinary cats. J Comp Neurol 1977; 173 (3): 497-518.

[133] Kliot M, Shatz CJ. Abnormal development of the retinogeniculate projection in Siamese cats. J Neurosci 1985; 5 (10): 2641-2653.

[134] Schall JD, Ault SJ, Vitek DJ, Leventhal AG. Experimental induction of an abnormal ipsilateral visual field representation in the geniculocortical pathway of normally pigmented cats. J Neurosci 1988; 8 (6): 2039-2048.

[135] Cooper ML, Blasdel GG. Regional variation in the representation of the visual field in the visual cortex of the Siamese cat. J Comp Neurol 1980; 193 (1): 237-253.

[136] Di Stefano M, Bedard S, Marzi CA, Lepore F. Lack of binocular activation of cells in area 19 of the Siamese cat. Brain Res 1984; 303 (2): 391-395.

[137] Girelli M, Campara D, Tassinari G, Marzi CA. Abnormal spatial but normal temporal resolution in the Siamese cat: a behavioral correlate of a genetic disorder of the parallel visual pathways. Can J Physiol Pharmacol 1995; 73 (9): 1348-1351.

[138] Marzi CA. Vision in siamese cats. TRENDS in Neurosciences 1980; 3 (7): 165-169.

[139] Holmes JM, Clarke MP. Amblyopia. Lancet 2006; 367 (9519): 1343-1351.

[140] Steeves JKE, Gonzales EG, Steinbach MJ. Vision with one eye: a review of visual function following unilateral enucleation. Spatial Vision 2008; 21 (6): 509-529.

[141] Gordon JA, Stryker MP. Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. J Neurosci 1996; 16 (10): 3274-3286.

[142] Fagiolini M, Pizzorusso T, Berson D, Domenicia L, Maffei L. Functional postnatal development of the rat primary visual cortex and the role of visual experience: dark rearing and monocular deprivation. Vision Research 1994; 34 (6): 709-720.

[143] Wiesel TN, Hubel DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. Journal of Neurophysiology 1963; 26 1003-1017.

[144] Blakemore C. The development of stereoscopic mechanisms in the visual cortex of the cat. Proc R Soc Lond B Biol Sci 1979; 204 (1157): 477-484.

[145] Kind PC, Mitchell DE, Ahmed B, Blakemore C, Bonhoeffer T, Sengpiel F. Correlated binocular activity guides recovery from monocular deprivation. Nature 2002; 416 (6879): 430-433.

[146] Blakemore C, Garey LJ, Vital-Durand F. The physiological effects of monocular deprivation and their reversal in the monkey's visual cortex. J Physiol 1978; 283 223-262.

[147] Blakemore C, Van Sluyters RC. Reversal of the physiological effects of monocular deprivation in kittens: further evidence for a sensitive period. J Physiol 1974; 237 (1): 195-216.

[148] Smith DC, Spear PD, Kratz KE. Role of visual experience in postcritical-period reversal of effects of monocular deprivation in cat striate cortex. Journal of Comparative Anatomy 1978; 178 (2): 313-328.

[149] Pizzorusso T, Medini P, Landi S, Baldini S, Berardi N, Maffei L. Structural and functional recovery from early monocular deprivation in adult rats. Proc Natl Acad Sci U S A 2006; 103 (22): 8517-8522.

[150] Tognini P, Manno I, Bonaccorsi J, Cenni MC, Sale A, Maffei L. Environmental enrichment promotes plasticity and visual acuity recovery in adult monocular amblyopic rats. PLoS One 2012; 7 (4).