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Chapter 12

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

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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]

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.

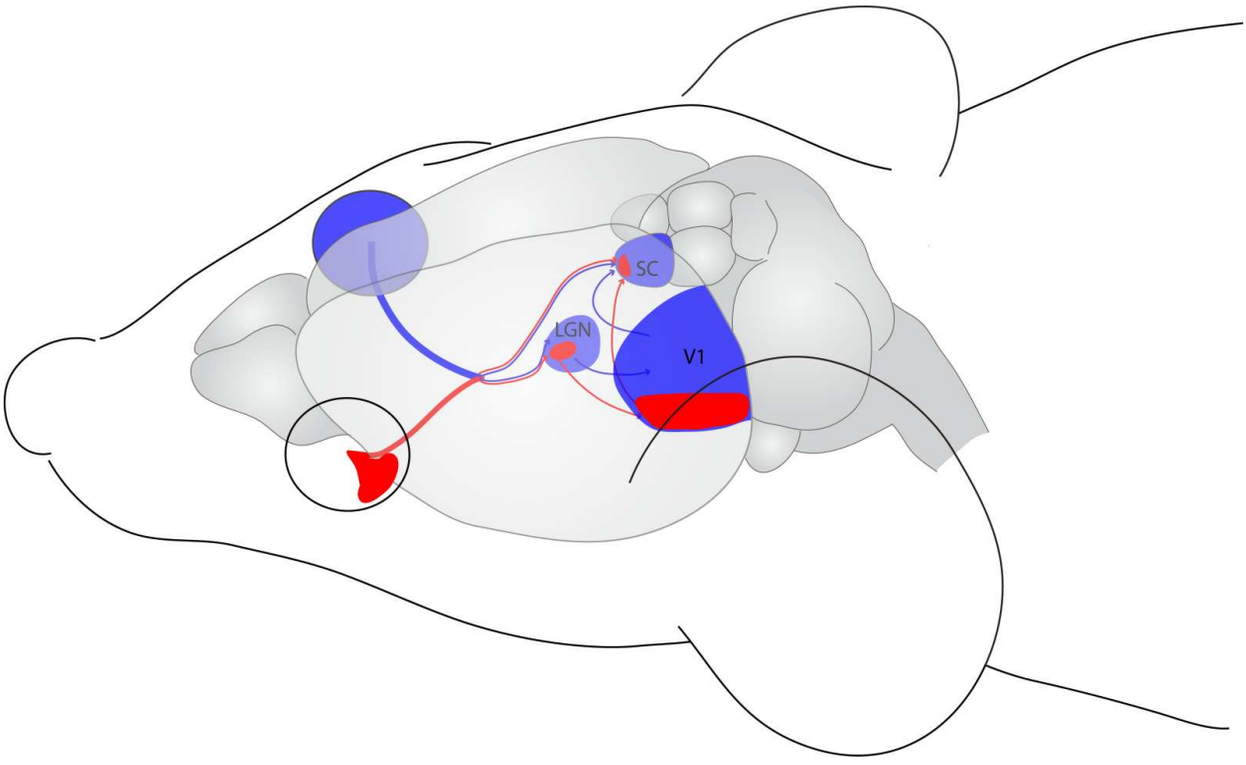

Figure 1. A schematic diagram of the main visual system circuitry in the mouse. dLGN= dorsal lateral geniculate nucleus, SC= superior colliculus, V1=primary visual cortex.

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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].

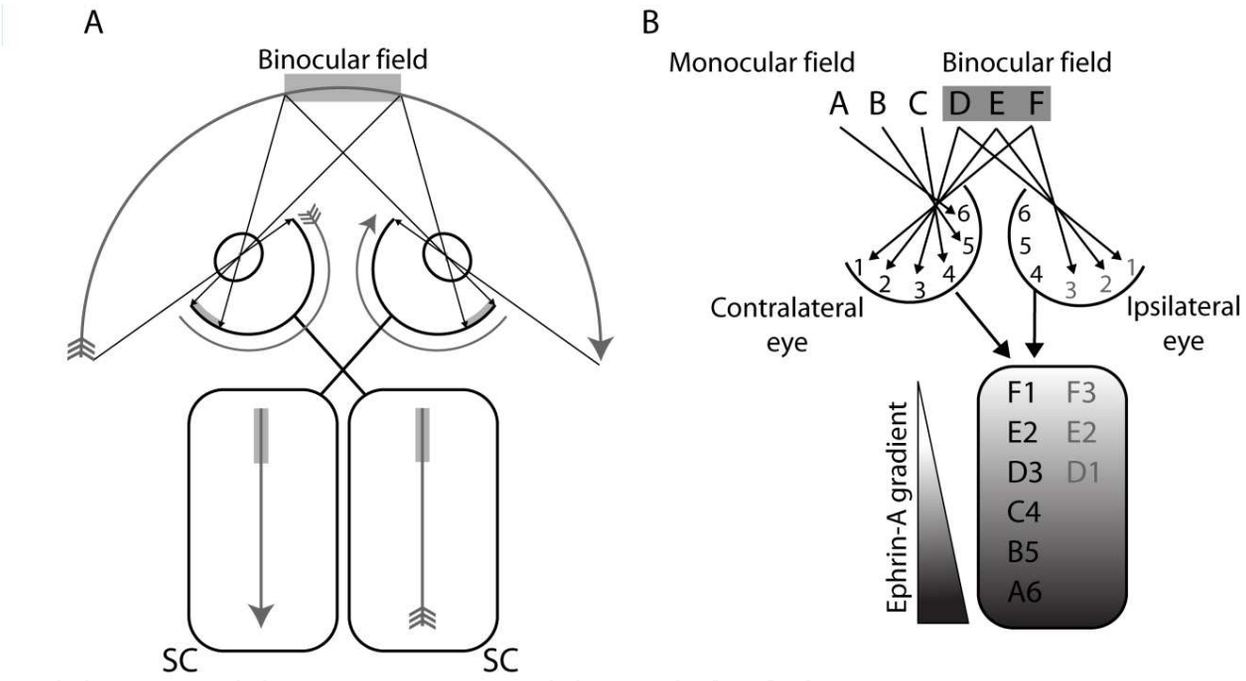

Figure 2. Monocular and binocular representation of the visual field in the superior colliculus (SC) in mice, modified from [2]. A: diagrammatic representation of visual field mapping across both SCs. B Diagrammatic representation of the integration of the ipsilateral and contralateral retinal projections 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-

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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

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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.

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