Seminars in Cell & Developmental Biology 35 (2014) 136–146

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Review

Activity dependent mechanisms of visual map formation - From retinal waves to molecular regulators

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ARTICLE INFO

Article history:
Available online 22 August 2014

Keywords:
Retinogeniculate
Retinocollicular
Activity
Ipsilateral
Contralateral
Development

ABSTRACT

The refinement of neural connections requires activity-dependent mechanisms in addition to the genetic program initially establishing wiring diagrams. The well-understood organization of the visual system makes it an accessible model for analyzing the contribution of activity in the formation of connectivity. Prior to visual experience, patterned spontaneous activity in the form of retinal waves has an important role for the establishment of eye-specific and retinotopic maps by acting on the refinement of axon arborization. In the present review, which focuses on experimental data obtained in mice and ferrets, we highlight the features of retinal activity that are important for visual map formation and question whether synaptic release and Hebbian based competition rules apply to this system. Recent evidence using genetic tools that allowed the manipulation of different features of neural activity have clarified the controversy on whether activity is instructive or permissive for visual map formation. Furthermore, current evidence strongly suggests that different mechanisms are at play for different types of axons (ipsilateral *vs.* contralateral), maps (eye-specific *vs.* retinotopic) or targets. Many molecules that either modulate activity or are modulated by activity are important in the formation of the visual map, such as adenylate cyclase 1, serotonin, or molecules from the immune system. Finally, new players in the game include retrograde messengers signaling from the target cell to the retinal axons as well as microglia that could help to eliminate inappropriate synapses.

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http://dx.doi.org/10.1016/j.semcdb.2014.08.008
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1. Introduction

Constructing precise neural circuits is a complex task. Molecular factors guide neurons to establish a primary scaffold that undergoes activity-dependent refinement to build a fully functional circuit. While the role of activity has been assumed for long, a clear demonstration of its effects has taken longer to demonstrate, raising a number of questions, such as determining where activity comes from, at a time when sensory experience is lacking. The finding that several systems display spontaneous activity during their developmental period [1–4] suggested that spontaneous activity could play a role in neural circuit refinement. In this regard, the visual system is an ideal model not only because retinal maps are sharply organized and their developmental sequences are well known but also because waves of spontaneous activity propagate within the developing retina [5,6] and are transmitted to the axons in the targets [7]. Many experiments manipulating retinal activity pharmacologically and genetically now demonstrate a role of this spontaneous activity on retinal maps. A controversy arose about whether this activity is instructive or permissive [8,9] but recent evidence has shifted the balance of arguments toward an instructive role. However, as will be discussed in the present review, the critical features of activity for shaping connections are still unclear. We focus our review on two lingering questions in the field which are how this retinal activity is transformed into molecular mechanisms that enable the cellular changes, such as axon retraction or branching that are involved in the refinement of neural circuits and what is the molecular control of activity-dependent mechanisms. Furthermore, recent experiments using genetic tools to manipulate activity have shown that activity can affect differently each visual map and thus, that the mechanisms at hand may be distinct. Following this new line, we here discuss each map separately to review the role of activity, upstream modulators, and finally the downstream targets that enact the refinement of these connections.

2. Organization and development of visual maps

The appropriate processing of visual information requires the correct organization of connections between the retina and the brain. Within the retina, numerous neuronal cell types integrate visual information, yet only the retinal ganglion cells (RGCs) convey this information to the brain. RGCs project to numerous brain nuclei [10] but their main targets are the dorsal lateral geniculate nucleus (dLGN) and the superior colliculus (SC). The dLGN is a relay nucleus that conveys information to the visual cortex for the image-forming pathway. The SC (sometimes referred also as the optic tectum in reference to the equivalent structure in other non mammalian vertebrates) is involved in non-image forming visual pathways, such as the control of head and eye-movements. In both targets, retinal axons organize in a topographic manner and ipsilateral and contralateral fibers innervate distinct regions (Fig. 1). The segregation into eye-specific territory (Fig. 1) is essential for binocular vision [11] while the topographic organization is crucial for a coherent representation of the external world.

2.1. Eye-specific map

In the mammalian brain, most visual centers receive afferents from both eyes. This level of organization of retinal inputs is referred to as the eye-specific maps. The initial step leading to eye-specific maps is the axon guidance choice of retinal ganglion cells (RGCs) at the optic chiasm to cross or not the midline, thus forming the contralateral and ipsilateral projections, respectively. In mice, RGCs projecting to the ipsilateral side are specifically located in the ventrotemporal (VT) retina and represent 3–5% of total RGCs [12]. Ipsilateral and contralateral axons travel in the optic tract and innervate first the dLGN and then the SC. In the dLGN, ipsilateral axons are located close to the center of the nucleus and surrounded by contralateral axons. Ipsilateral and contralateral terminals are segregated from each other and form an eye-specific map (Fig. 1). The degree of overlap between ipsilateral and contralateral axons in the dLGN is often used to measure the level of refinement of retinal axons and serves as a read-out for axonal refinement and synaptogenesis. In the SC, ipsilateral and contralateral projections are also segregated from one another, as they target different layers (Fig. 1). Contralateral axons are essentially localized in the most superficial layer of the SC, the stratum griseum superficiale (SGS), while the ipsilateral axons are located in the underlying layer, the stratum opticum (SO). Furthermore, ipsilateral axons are distributed along the full extent of the mediolateral axis in the rostral SC where they form aggregated patches and are restricted to a single medial patch in the caudal SC (Fig. 1). The most classic way to observe eye-specific domains is to use ocular injection of anterograde tracers, originally horse radish peroxidase (HRP) and nowadays, cholera toxin beta subunit (CTB) coupled with different AlexaFluor dyes to label projections coming from both eyes with different colors.

The development of the eye-specific maps has been well established. First, RGCs extend their axon out of the retina to reach the optic chiasm between E12 and P0 [13] and reach the dLGN at E16 and SC from E18 in mice [14]. Even though ipsilateral axons arrive early at the optic chiasm (E12–E17) they innervate and spread within the dLGN only from P0 [14], suggesting a waiting mechanism or a slower growth or branching compared to contralateral axons. Initially, ipsilateral and contralateral axons overlap in the dLGN but start to segregate into distinct domains from P4 [14] (Fig. 2). By P8, ipsilateral and contralateral inputs are mainly segregated with ipsilateral projections forming a “patch” mostly devoid of contralateral axons (Fig. 2). At that age, however, one thalamic target still receives inputs from both eyes [15]. At P15, the eye-specific domains are similar to those in adult (Fig. 2) and one thalamic target cell receives now inputs only from one eye [15]. Thus, eye specific segregation involves a synapse selection with elimination of misplaced synapses and maintenance of proper synapses.

The developmental sequence is somewhat similar in the SC, with a progressive elimination of ipsilateral inputs in the most superficial layers, although ipsilateral axons do not invade completely the SGS even before P3, and are mainly eliminated by P8 [14,16]. Thus, in the SC, the overlap of ipsilateral and contralateral retinal inputs is not as important as in the dLGN possibly because other molecular factors set up a laminar organization in parallel to the segregation of ipsilateral and contralateral axons, preventing a complete overlap.

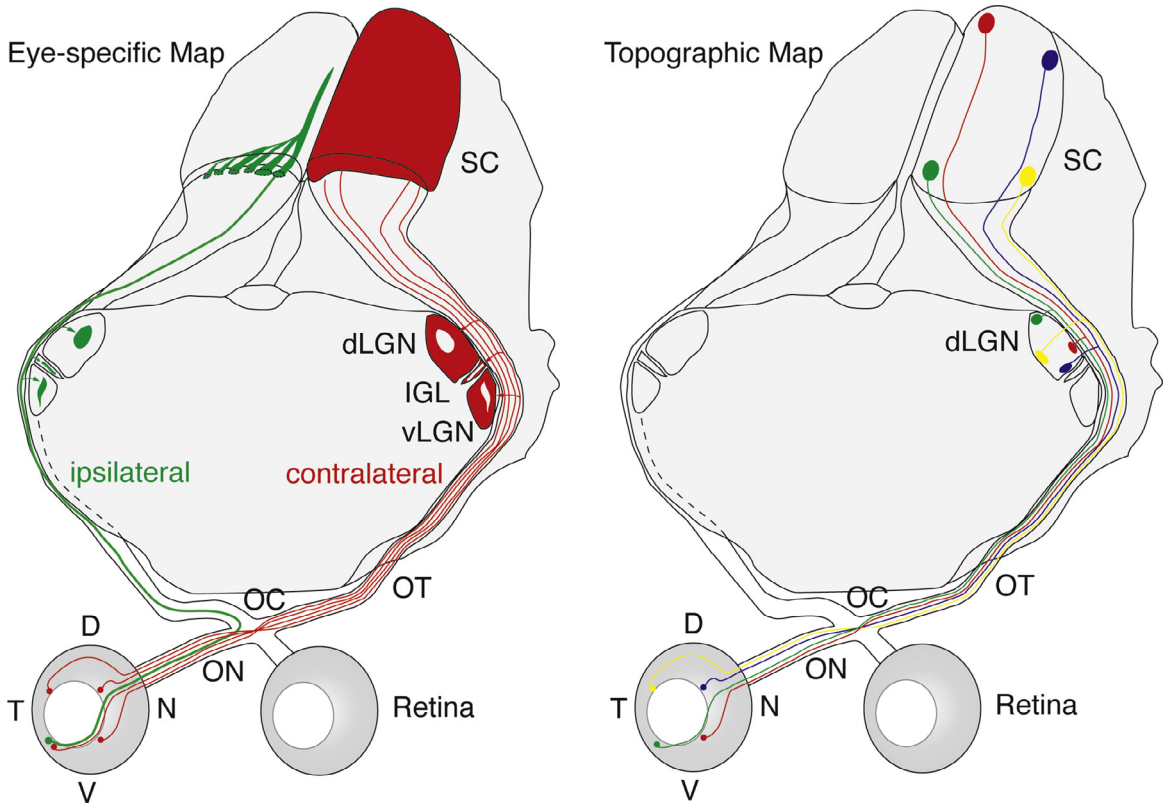

Fig. 1. Organization of retinal projections into eye specific and topographic maps in the mouse visual system. ON: optic nerve, OC: optic chiasm, OT: optic tract, vLGN: ventral lateral geniculate nucleus, dLGN: dorsal lateral geniculate nucleus, IGL: intergeniculate leaflet; SC: superior colliculus, D: dorsal, N: nasal, V: ventral, T: temporal.

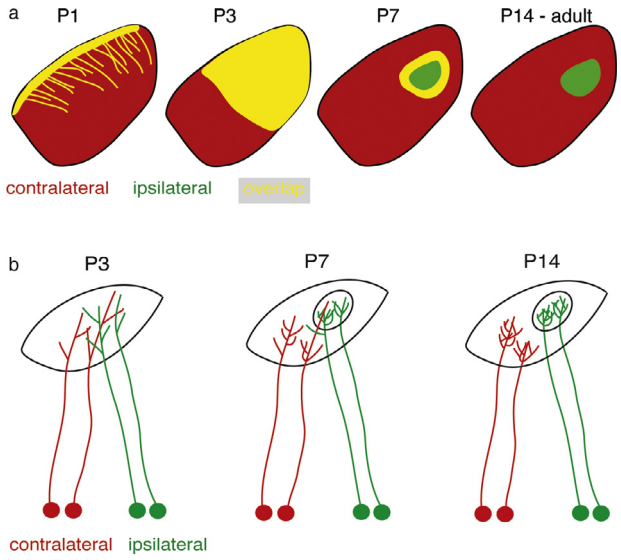

Fig. 2. Eye-specific refinement of retinal axons during development. (A) Developmental sequence of eye-specific retinogeniculate map formation. At P1, contralateral axons are distributed in the entire dLGN and ipsilateral axons start to invade the dLGN. At P3, ipsilateral and contralateral axons overlap on a large portion of the dLGN. At P7, contralateral axons have started to retract from the ipsilateral region, leaving a gap that is innervated by ipsilateral axons. Eye-specific segregation is thus visible. At P14, contralateral and ipsilateral axons are clearly segregated into different domains and show an adult-like pattern. (B) Developmental sequence of axonal refinement in the dLGN based on single axon reconstruction of ventrotemporal axons. At P3, ipsilateral and contralateral axons are intermingled and their arbors are simple. At P7, ipsilateral and contralateral axons have more elaborated branches and start to arborize preferentially in a distinct domain. By P14, ipsilateral and contralateral axons have a very dense arborization and no ectopic branches are visible.

2.2. Retinotopic map

Retinal axons are topographically distributed: the nasotemporal axis in the retina projects to the caudo-rostral axis in the SC, and the dorso-ventral axis in the retina to the latero-medial axis in the SC (Fig. 1). Most studies of retinotopy focus on the retinocollicular (or retinotectal) projections as retinal projections are organized mainly in two dimensions (rostro-caudal and medio-lateral) which facilitates tracking of defects, however, the retinogeniculate projections in the dLGN are also organized in a topographic manner, but the three-dimensional organization renders it more difficult to examine (Fig. 1). Roughly, the nasotemporal retinal axis maps onto the ventrolateral–dorsomedial axis of the dLGN, and the dorsoventral retinal axis maps along the ventromedial–dorsolateral axis of the dLGN [17,18]. This topographic organization is specific to the contralateral projections but ipsilateral axons also target specific regions. The contralateral VT RGCs project to the dorsal tip of the dLGN and the rostromedial part of the SC while the ipsilateral VT RGCs project to a similar topographic region but slightly shifted ventrally in the dLGN and caudally in the SC [17,19]. The easiest way to examine topographic organization is to achieve small injections of DiI into different retinal quadrants and to observe their projection most often in the SC but also in the dLGN.

The development of retinotopic ipsilateral and contralateral maps is determined by gradients of repulsive guidance molecules from the ephrin family (ephrin and Eph receptor) that are expressed in RGCs and targets and indicate a positional information based on repulsive interactions [20] see in this issue, review by Franco Weth. The maturation of the topographic maps comprises different sequential steps [21,22]. First, retinal axons distribute in the entire target, then gradients of Eph/ephrins position encode the proper localization of the termination zone (TZ) according to the retinal position (Fig. 3). Second, the axonal arborization is refined with the

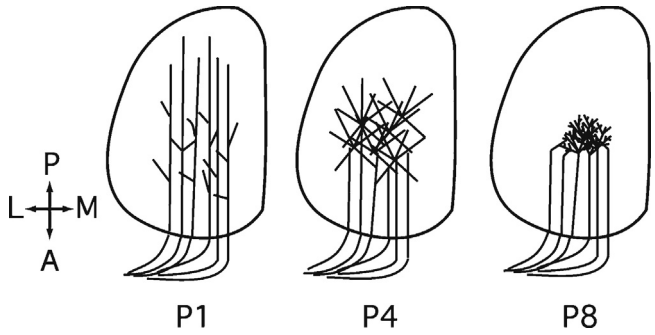

Fig. 3. Topographic refinement of retinal axons during development. Developmental sequence of topographic retinocollicular map formation. Temporal axons are distributed along the entire SC at P1, then form branches around the appropriate topographic location in the rostral part of the SC with some overshooting axons already retracted at P4. At P8, temporal axons are branching specifically in the terminal zone and all ectopic axons are pruned.

retraction of abnormal collaterals and there is an increased branching and synapse formation in the correct location (Fig. 3). Finally, there is a fine scale refinement of retinotopy after eye-opening as electrophysiological recordings indicate that one geniculate neuron receives inputs from more than 10 RGCs at P8-P10 and only 1–3 RGCs after P18 [15,23].

2.3. Axonal arborization and collaterals

In mice, a given RGC can innervate both the dLGN and the SC, by a collateral branching out of the optic tract [24]. Single RGC labeling techniques *in vivo* allowed to follow the refinement of single RGC arbor during development [25]. Retinal axons often overshoot their final topographic zone with temporal axons projecting to the caudal SC for instance [21,24,26,27] (Fig. 3). Interestingly, there is a temporal mismatch between the maturation of contralateral axonal arbors in the dLGN and the SC, with axon arbors being more complex one week earlier in the SC than in the dLGN [24]. Thus, by P8, retinogeniculate axons only start to branch (Fig. 2B) while retinocollicular axons are already fully branched already with an adult like pattern (Fig. 3). While this temporal mismatch is observed for contralateral axons, ipsilateral axons in both dLGN and SC mature later similarly to contralateral axons in the dLGN. This suggests that the maturation of axon arbor relies on mechanisms that are different depending on the target (dLGN or SC) and eye of origin (ipsilateral or contralateral).

3. Spontaneous retinal waves

The role of neural activity on visual circuit development started initially with studies in cats and ferrets examining effects of visual inputs on neural circuit development, with experiments such as monocular occlusion [28] or changing ocular stimuli [29]. It was only recognized later that non-visually driven neural activity could contribute to early activity-related mechanisms and the shaping of neural connectivity.

The existence of spontaneous activity in the retina was described for the first time by *in vivo* recordings of action potentials in the retina of rat embryos [2]. Calcium imaging and multielectrode array studies further detailed the temporal and spatial characteristics of this spontaneous retinal activity [5,30], showing that it starts from random initiation sites, in the retina followed by a propagation to neighboring cells, creating a spreading pattern of spontaneous activity, called “retinal waves”. The details of retinal waves have been extensively reviewed [31,32]. Waves initiate every 25 s (in a domain >1 mm^2), propagate in restricted domains and are followed by refractory periods of RGCs (25–35 s) [33]. This low frequency would enable neighboring RGCs to show correlated activity [5,6].

Three different stages of spontaneous retinal activity have been described [31]: gap junction-mediated activity waves (stage I) occurring before birth, acetylcholine (ACh) mediated waves (stage II) occurring mostly during the first postnatal week and glutamate mediated waves (stage III) occurring during the second postnatal week. Visually evoked activity starts around P11 with photoreceptors functionally connected to the retinal network. Stage II waves have been the most studied: they are driven by starburst amacrine cells which fire spontaneously, release ACh and depolarize neighboring amacrine cells and RGCs expressing ACh receptors (AChR). Stage III retinal waves are driven by bipolar cells which release glutamate and trigger activity in neighboring RGCs.

Importantly, spontaneous retinal activity is transmitted from RGCs to their targets and has been imaged by genetically encoded calcium indicators *in vivo* [7]. It is also noteworthy that the retinal waves are not completely random as they initiate preferentially from the VT retina which corresponds to the binocular region and propagate preferentially toward the dorsonasal retina *in vivo* [7]. The fact that stage II and III retinal waves coincide with visual map establishment suggested a role of spontaneous activity in retinal projection development.

4. Role of activity on visual map formation

4.1. Role of activity on eye specific segregation

The role of activity has been assessed in many different experimental conditions, blocking activity in either the eye or targets with pharmacological agents or with genetic tools, leading sometimes to controversy in the field that we briefly overview here.

Early experiments analyzing the effects of activity used the voltage-gated sodium channel blocker, tetrodotoxin (TTX), which inhibits both firing of action potentials and propagation of nerve impulse. TTX infusion around the optic nerve in cats induced eye-specific segregation defects in the dLGN [34,35]. However, TTX infusion in the eye did not impair eye-specific segregation in the ferret dLGN [36] nor eye specific lamination defects in the rodent SC [37,38], which seemed to disprove a role for activity in eye-specific segregation. However experiments using TTX *in vivo* are hard to interpret because of the toxicity of the compound, making it hard to have an effective and yet non-toxic dosage.

Subsequent experiments analyzing the role of activity focused on a more specific removal of retinal waves focusing on the cholinergic system, to inhibit pharmacologically the nicotinic receptor with epibatidine, or to remove the beta2-acetylcholine receptor (beta2-AChR), the subunit of nicotinic receptor that appears to mediate the main cholinergic drive of RGCs. In both models, blockade of nicotinic transmission was found to cause clear eye-specific segregation defects in the dLGN and the SC (Fig. 4A). In epibatidine-treated mice or ferrets and in beta2-AChR KO mice, contralateral retinal projections cover the entire dLGN, including the ipsilateral territory and ectopic ipsilateral projections are present within the contralateral territory (Fig. 4A) [19,39,40]. In the SC of beta2-AChR KO mouse, ectopic ipsilateral projections are present in the contralateral territory (SGS), instead of being restricted to the SO, such that ipsilateral and contralateral projections still overlap (Fig. 4A) [40,41]. In beta2-AChR KO mice and epibatidine-treated ferrets, eye specific segregation is partially rescued during later phases of development [40–43], possibly because of later glutamatergic retinal waves. Single axon reconstructions in beta2-AChR KO mice at P15 show that contralateral retinal axons display normal terminal arbors in the dLGN [24] although their topographic position remains abnormal [42,43]. Similarly, when beta2-AChR KO mice

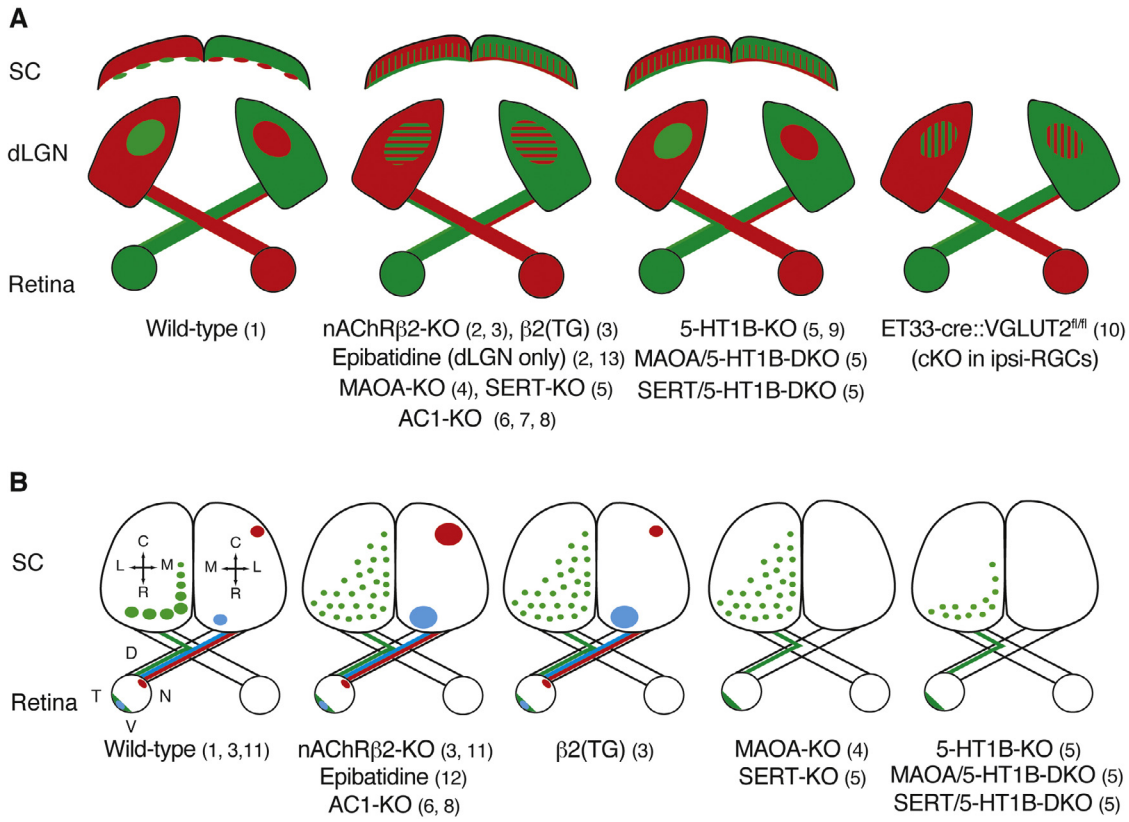

Fig. 4. Effects of activity perturbations on eye specific (A) and topographic (B) organizations in different mouse models. (A) Schematic representation of whole retinal projections coming from the left eye (green) and right eye (red) in the dLGN and in the rostral SC at P10-15 and in adults. Hatched regions correspond to regions where red and green axons from the two eyes overlap. (B) Topographic organization of ipsilateral projections and contralateral projections on a dorsal view of the SC. Whole ipsilateral projection was labeled (in green) while focal injections to the ventro-temporal retina (in blue) or to the dorso-nasal retina (in red) were done to label contralateral projections. 1: Godement et al. [14]; 2: Rossi et al. [40]; 3: Xu et al. [41]; 4: Upton et al. [99]; 5: Upton et al. [101]; 6: Ravary et al. [78]; 7: Nicol et al. [27]; 8: Dhande et al. [80]; 9: Salichon et al. [100]; 10: Koch et al. [52]; 11: McLaughlin et al. [22]; 12: Chandrasekaran et al. [62]; 13: Rebsam et al. [19]. AC1: adenylate cyclase 1, β2 (TG): beta2 subunit transgene expressed in retina of nAChR β2-KO, cKO: conditional knockout, DKO: double knockout, dLGN: dorsal lateral geniculate nucleus, 5-HT1B: 1B serotonin receptor, KO: knockout, MAOA: monoamine oxidase A, nAChR β2: beta2 subunit of the nicotinic acetylcholine receptor, RGCs: retinal ganglion cells, SC: superior colliculus, SERT: serotonin transporter, VGLUT2: vesicular glutamate transporter 2, C: caudal, L: lateral, R: rostral, M: medial, D: dorsal, T: temporal, V: ventral, N: nasal.

and epibatidine treated ferrets, reach adulthood, there is both an electrophysiological and anatomical rescue of eye-specific segregation [43,44]. However, eye-specific segregation is still perturbed in epibatidine-treated mice at P31 [19].

The rescue of eye-specific segregation in the beta2-AChR KO mice indicated the importance of the third glutamatergic retinal waves during the second postnatal week. Other experiments indicated that late perturbation of these glutamatergic waves could indeed induce a desegregation of eye-specific projections in the dLGN and the SC [45–48]. Interestingly, in all these studies, only the ipsilateral projections showed a *de novo* sprouting, invading the contralateral territory, whereas the contralateral projections seemed not to be plastic beyond the first postnatal week. Thus, contralateral projections mislocated because of perturbations during the first postnatal week are not rescued later and activity perturbation after the first postnatal week has no effect, suggesting a critical period for the positioning of contralateral projection during the first postnatal week.

Altogether, these data suggest that normal RGC activity is important for eye specific map establishment, eye specific segregation and eye specific domain positioning, but the critical periods are not the same for each event. Also the critical periods of plasticity for ipsilateral and contralateral projections are different: ipsilateral projections are plastic until later ages than contralateral projections.

Other sets of experiments have investigated the role of activity-dependent competition, rather than blocking overall activity. The hypothesis explored is that there is a balance between axons coming from both eyes and that modifying activity in some axons will perturb this balance. Enucleation experiments in rats, hamsters and mice showed that removal of one eye leads to the expansion of the projections coming from the remaining eye [37,38,49], suggesting that indeed there is a competition between ipsilateral and contralateral projections to occupy a specific territory. However, the enucleation is a rather crude experiment, and does not only affect activity but also the availability to trophic factors. Activity dependent competition was assessed in studies in which activity was altered specifically in one eye: monocular epibatidine injection (reduced activity in the treated eye) [39] or monocular injection of a cAMP agonist (increased activity in the treated eye) [50] lead to the expansion in the ferret dLGN of the projections coming from the more active eye. However, eye specific segregation is not modified in such experiments, the contralateral projections enlarge but do not invade the smaller ipsilateral territory corresponding to the less active eye. These experiments strongly suggest that activity based competition is required for determining the size of the eye-specific projections. These effects of activity could also reflect a modified uptake of trophic factors such as BDNF that influence both RGC survival and branching.

4.2. Role of synaptic release on eye-specific segregation

While the role of retinal activity in the establishment of eye-specific retinal projections has now been clearly demonstrated by

the experiments described above, the downstream mechanisms are unknown. One logical mechanism is the conversion of this electrical activity into calcium dependent synaptic release at axon terminals. Functional synapses are already present in the targets during eye specific segregation [51]. Recent experiments showed the requirement of glutamate synaptic release in ipsilateral projections to exclude the contralateral projections using the VGlut2 conditional KO [52]. In this model, glutamate release was impaired specifically in ipsilateral axons but the main effect observed was that contralateral axons did not retract from the ipsilateral territory (which was normal in size) (Fig. 4A). This suggests that synaptic release from ipsilateral axons modifies the presynaptic terminals of contralateral axons, either by a direct effect of transmitter release on presynaptic axons or *via* postsynaptic receptors on the target cells involving a retrograde signal sent to the contralateral axons. Which postsynaptic receptors could be involved in the formation of eye-specific segregation? One ideal candidate for plasticity events linked to glutamate release is the NMDA receptor, which acts as a "coincidence detector", as the neuron has to be depolarized for the receptor to function. In frogs, all the projections cross the midline and project contralaterally in the tectum (SC equivalent). Grafting a third eye inducing stripes in the tectum with projections coming from this grafted eye segregated from the ones coming from the normal eye [53] due to selective branch elimination [54]. NMDA receptor antagonists in this system induce a desegregation of these projections [55] by preventing branch elimination [54]. However, NMDA receptor blockade does not impair eye-specific segregation in the ferret dLGN [56] and in the rat SC [57]. It is possible that other postsynaptic glutamate receptors are also involved in the segregation process, since there is still correlated retinal induced firing in the dLGN cells in the absence of NMDA receptors [51]. Moreover, mice with perturbed levels of L-type Ca2+ channels display eye-specific segregation defects [58] suggesting the importance of this type of channels. Thus, the role of synaptic release from RGCs to their targets seems to be important but the postsynaptic receptors involved still need to be identified.

4.3. Role of activity on retinotopy

The position of the retinal axons along the antero-posterior axis of the SC has been shown to depend largely on ephrin-EphA signaling [20] (Franco Weth, in this issue). Neural activity was shown to modulate the response of RGCs to ephrins and thereby influence the retraction of inappropriately located axons. *In vitro*, the collapse response of RGCs to ephrins is arrested by acute TTX application and TTX prevents the normal topographic refinement of temporal and nasal retinal explants in a retino-collicular co-culture where the refinement of nasal axons in the caudal SC and temporal axons in the rostral SC is reproduced [59]. *In vivo* data however, do not seem to confirm, so far, the involvement of activity for the final topographic positioning of RGCs. Monocular TTX injections, did not impair the retraction from the caudal SC of temporal RGCs [60] and expression of inward-rectifier potassium ion channels (Kir2.1) in the mouse retina (which blocks activity by membrane potential hyperpolarization) did not induce major targeting defects of retinal axons in the SC [61].

In beta2-AChR KO and epibatidine-treated mice, retinal projections were broader but located at the right topographic TZ (Fig. 4B) [22,41,44,62]. This defect can be explained by ectopic branches along the axon and larger terminal arbor in beta2-AChR KO [24] a feature also observed after TTX blockade [59] or Kir2.1 expression [61]. In the beta2-AChR KO, a partial rescue of the TZ size refinement shown in the SC occurs between P7 and P14 [24,62]. Although single axon reconstruction show no major defects [24], TZ in the dLGN and SC are enlarged, reflecting the fact that neighboring RGCs do not converge on the same TZ contrary to controls [22,41]. Overall these results suggest that early RGC activity is intrinsically important for the maturation of the RGC terminal arbors and act on the precise position of TZ at a very fine scale level.

The fine scale retinotopic refinement corresponding to stage III retinal waves was revealed by anatomical and electrophysiology recordings: single thalamic neurons receive weak inputs from 10 to 30 RGCs at P7 and only from 1 to 3 RGCs by P14 [15,23,63]. Retinal activity blockade by TTX between P11 and P14 impairs this fine scale refinement [63]. Single axon reconstructions between P9 and P15, showed an increase in the number of branch points [24] suggesting an increase in synaptic contacts. Thus, at the presynaptic level of a RGC terminal arbor, the fine scale refinement is due to both an elimination of synapses from most of the postsynaptic cells in parallel with an important elaboration of synapses on few postsynaptic cells.

Overall, these data indicate that although retinal activity modulates axon guidance, the effects are not crucial for the global topographic positioning of RGCs *in vivo* but are more likely to affect the size/extent of the RGC terminal zones (TZ).

4.4. Role of synaptic release on retinotopy

Is synaptic release from RGCs to their targets important for retinotopy refinement? The global topography is normal in retinocollicular co-cultures using Munc18-1 KO retinal explants, that have no synaptic release, or using pharmacological blockade of NMDA or AMPA receptors contrasting with the effects of TTX, suggesting that ordering of retinal projections is activity-dependent but not dependent on presynaptic release [59]. However later stages of refinement may require synaptic mechanisms since NMDA receptor blockade in hamster and rat SC leads to enlarged receptive fields in the SC [64,65]. Whether presynaptic release and NMDA receptors are required for topographic map is thus still an open question.

4.5. Instructive vs. permissive role of activity

While the role of activity on the formation of retinal maps is now widely accepted, its precise role is still debated and especially whether activity is permissive or instructive for retinal projection development [8,9]. "Permissive" implies that only the presence of activity is required while "Instructive" implies that the patterns of activity contains information necessary for the development of visual maps. This later hypothesis is very attractive as spontaneous retinal waves through their various spatio-temporal features can code information meaningful for the refinement of retinal axons. Since the spontaneous retinal waves trigger correlated activity within groups of neighboring RGCs, they are ideal candidate to underlie eye-specific segregation and retinotopy refinement through Hebbian synaptic rules. Burst time-dependent plasticity can be elicited at retinogeniculate synapse in rats [66] and retinocollicular synapse [67] suggesting that Hebbian type rules can apply to these synapses. If activity is indeed instructive, changing the pattern of activity or the correlation of neighboring RGCs without modifying the overall level of activity should be sufficient to alter visual system development. However, this has proven very difficult to achieve as most models end up changing both the spatio-temporal pattern of activity and the global level of activity as is the case for epibatidine-treated mice and beta2-AChR KO mice [33,41,68,69] that showed similar defects in both eye-specific segregation and retinotopic refinement (Fig. 4) [22,40,42,44,62]. An interesting study eliminated starburst amacrine cells by using an immunotoxin in the ferret postnatal retina [70] and showed normal eye-specific segregation suggesting that retinal waves were not required. However, the initial report that neighboring RGC activities were decorrelated in this model [70] was later disproven

as retinal waves were found to be still present, although with a lower correlated activity of neighboring RGCs [71]. These results have been extensively discussed in two previous "viewpoints" [8,9]. Interestingly, two other recent models pertain to this question. A transgene of the beta2-AChR subunit has been specifically expressed in RGCs in the full beta2-AChR to rescue the expression of beta2-AChR only in RGCs. In this model (beta2TG), RGCs have a normal level of activity but retinal waves are modified (they are smaller and with different number of bursts per wave) [41]. The beta2TG mice show a rescue of the major retinotopic defects in the dLGN and SC but no rescue of the eye-specific segregation deficits (Fig. 4) found in the beta2-AChR mice, suggesting that a normal level of activity is not sufficient for proper eye-specific segregation and thus fitting with the idea of an instructive role of activity. The limiting factor seems to be the size of the waves but this will need to be proven by other experiments in the future. Interestingly, retinotopic defects are maintained in the binocular region in both the dLGN and SC of beta2TG mice, and these defects are rescued by a monocular enucleation [41]. The latter result suggests that the alteration of eye-specific maps could impact the proper refinement of retinotopic maps in the binocular zone and thus points to an interplay between ipsilateral and contralateral inputs for the establishment of both maps, an interesting notion that will need further confirmation.

Another model used optogenetic tools to manipulate the pattern of retinal activity using channel-rhodopsin ChR2 in RGCs with light-induced synchronous or asynchronous stimulation from P5 to assess eye-specific segregation at P9 [48]. Synchronous stimulation of both eyes, induced a mild desegregation of eye-specific maps, while asynchronous stimulation enhanced slightly the segregation in the SC [48]. These results suggest that the relative timing of activity in the two eyes mediates the non-retraction and/or sprouting of ipsilateral axons, suggesting that activity has an instructive role through Hebb-based activity dependent competition for this phenomenon and also highlight that mechanisms could be different in the dLGN and SC.

5. Other factors involved in visual map formation and linked to activity

5.1. Retinal ganglion cell death

Refinement of eye-specific and retinotopic maps coincides with a period of massive developmental cell death. Up to 50% of RGCs are lost due to cell death, between P0 and P7 in mice, while at the same time period amacrine cells and photoreceptors are increasing in numbers [72,73]. Early studies of O'Leary et al. [60] showed that the postnatal removal of erroneously positioned retino-collicular axons (Fig. 3) could be due to developmental cell death in an activity-dependent manner. These experiments were done in rats using a clever combination of tracer and TTX injections at different developmental times. More recently, TTX application in the retino-collicular model showed that TTX reduced both the topographic refinement and developmental cell death of RGCs, further supporting this hypothesis [59,73]. However, arguments against a requirement of cell death for the specific modeling of retinal maps came from genetic experiments in which the anti-apoptotic molecule Bcl-2 was overexpressed; in Bcl2-Tg mice, normal maps were noted despite the substantial decrease in cell death [74]. However, it is likely that activity acts on cell death for population matching and could play a role in activity-dependent competition for retinal targets. For instance, BDNF, whose expression is increased by neural activity in retinal targets [75], can selectively increase the survival of ipsilateral RGCs although it has no effect on total RGC survival [76]. Thus, activity-dependent cell death contributes to the elimination of RGCs during this developmental time window but does not appear to be the main factor to eliminate RGCs with inappropriately located arbors.

5.2. Adenylate cyclases

One of the important questions raised when considering the effect of neural activity on neural circuit patterns is to understand how changes in the intensity/frequency of action potentials are converted into morphological changes of axon terminals. One of the obvious downstream signals is calcium that enters the cells *via* voltage-gated channels, triggering molecular cascades that involve cAMP and PKA-dependent mechanisms. Interesting candidates in this respect are the calcium-dependent adenylate cyclases (AC) [77]. Several isoforms of AC have been demonstrated in the developing rodent retina but only one, AC1, was shown to be required for retinal map development [78,79]. AC1-KO mice have similar eye specific segregation and retinotopic refinement defects as the beta2-AChR KO (Fig. 4) [78–80]. However, unlike the beta2-AChR KO, AC1-KO mice have normal retinal waves [80] and there is no late rescue of the segregation defects [42,78]. This suggests that AC1 could transduce the electrical activity in RGCs (action potentials) into chemical signals within the neuron during the stage II and III retinal waves. Because AC1 was shown to be required in the RGCs and not in the targets for retinal map refinement [27], possible effects of changes in cAMP signaling in the growth cones were investigated. Although the general topography of the map was unaltered in the AC1-KO, lack of AC1 changed the response of RGCs to ephrin-A5 in an unexpected way [27]. Although the initial collapse response to ephrins was not modified, the retraction of the AC1-KO RGC growth cone was arrested in comparison to controls, indicating an interaction with the cytoskeletal mechanisms involved in axon pruning. Other components of the ephrin-A5 signaling, such as effects on axon branching were not modified in the AC1-KO. Single axon reconstructions showed a normal branching complexity of terminal arbors [27,80], although aberrant ectopic axonal branches were maintained, suggesting a main effect on the pruning back.

In addition to these local effects on axons, activity-triggered cAMP signals could have effects on gene transcription. Although such changes were not reported in the AC1-KO, other studies analyzing cAMP-response element binding protein (CREB) mutant mice showed an abnormal eye-specific segregation [81]. However, the mechanisms underlying these changes remain to be clarified.

5.3. Retrograde signaling

Refinement of retinal projections likely involves retrograde signaling from the target cells to influence synaptic maintenance or removal of retinal terminals. Three potentially important candidates are listed below.

The endocannabinoids (CBs) are released by post-synaptic cells in an activity-dependent manner and activate pre-synaptic cannabinoid receptors (CB1R and CB2R). Interestingly, they can mediate short-term depression (STD) and long-term depression (LTD) [82,83] that could lead to synapse elimination. The different components of the endocannabinoid system are expressed in the visual system and it has been shown by *in vitro* and *in vivo* experiments, that they could play a role in axon guidance and eye specific segregation of retinal projections in the SC and the dLGN [84–86].

Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and their receptors such as TrkB are another class of important molecular signals regulated by activity. In the visual system, BDNF and TrkB are important to protect RGCs and target cells (SC and dLGN) from cell death and from retinal projection retraction [87–90]. BDNF/TrkB signaling modulates glutamatergic synapses

through pre and post-synaptic mechanisms [91,92]. However, both BDNF-KO mice [92] and TrkB KO mice [90] displayed normal eye specific segregation in the SC or the dLGN. Importantly, TrkB KO mice have an ectopic ipsilateral projection caudally in the SC [90].

Nitric oxide is another potential retrograde signal. Pharmacological inhibition of calcium sensitive nitric oxide synthase (NOS) in ferrets did not impair eye specific segregation dLGN [93]. In contrast, genetic approaches of NOS inhibition leads to ectopic ipsilateral projection caudally in the SC of NOS KO mice [16] and in the SC of NOS inhibitor treated rats [94], but without clear defects in eye specific segregation.

Overall, these retrograde signals seem to participate in the refinement of the ipsilateral projection but their precise role in the activity-dependent mechanisms is still in need of further investigation.

5.4. Serotonin

Serotonin (5-HT) neurotransmission has emerged as an important actor of activity-dependent refinement of retinotopic and eye-specific maps with effects that are essentially localized at the presynaptic level. The role of 5-HT was initially shown in hamsters with increased brain 5-HT level due to aberrant sprouting of 5-HT innervation after neonatal administration of the neurotoxic 5–7 DHT [95]. This treatment was shown to alter the organization of both the crossed and uncrossed retinotectal map with an enlargement of visual receptive fields [96]. More direct evidence for a causal role of 5-HT came from genetic mouse models lacking monoamine oxidase A (MAOA), the degradation enzyme for monoamines, or the 5-HT transporter (SERT) [97–99]. In these two genetic models, eye-specific segregation in the dLGN is altered and ipsilateral fibers in the SC do not cluster and extend beyond their normal territory (Fig. 4) [95,99,100]. The overactivation of 5HT1B receptors by 5-HT excess is responsible for most defects as double-mutant for MAOA or SERT and 5-HT1B have a mostly rescued phenotype (Fig. 4) [100,101]. Interestingly, 5HT1B receptors are presynaptic, expressed in all RGCs [99,102] and exert a strong inhibitory control on glutamatergic transmission [102]. Thus a main effect of overstimulation of the 5-HT1B receptors would be to inhibit neurotransmission at the retinotectal and retinogeniculate synapses. This leads to phenotypes that are very similar to the ones observed in the beta2-KO and the AC1-KO (Fig. 4): at least as concerns the eye-specific segregation, and the lack of refinement of the ipsilateral retinal projections. Interestingly, 5HT1B-KO mice have no defects in eye-specific segregation or topographic refinement, except for the refinement of ipsilateral axons in the SC (Fig. 4) [101] suggesting that this receptor is crucial for their proper refinement independently of the 5-HT levels.

Interestingly, features of the serotoninergic system are expressed transiently by glutamatergic neurons of sensory systems during development, in retinal axons [99]. These serotoninergic characteristics include the 5-HT transporter (SERT) and the vesicular monoamine transporter (VMAT2) but not the enzymes for 5HT synthesis [99]. Strikingly, SERT is transiently expressed mainly in the ipsilateral but not contralateral RGCs located in the VT retina [99]. Although the specific function of SERT in these cells is still unknown, it has been demonstrated that SERT expression allows a high affinity uptake of serotonin in the ipsilaterally projecting RGCs [99]; yet SERT did not appear to be required for axon guidance at the midline [103]. SERT-KO show visual map defects (Fig. 4) but it is difficult to assess SERT's specific role in RGCs independently of its more general effects on brain 5-HT levels [100,101]. A possible hypothesis is that SERT in ipsilateral RGCs locally modulates 5-HT concentration by clearing 5-HT from ipsilateral synapses. This could induce different local concentrations of 5-HT causing a difference in the neural activity/release properties of the ipsi/contralateral RGCs. However, 5-HT could also act directly on retinal axons, or through the modulation of response to guidance cues [104,105], independent of neurotransmission. Even though serotonin and 5HT1B receptor are clearly important for visual map formation, the specific cellular aspects that are modulated by 5-HT signaling for retinal refinement remain to be determined.

5.5. Immune system molecules, glia and microglia

An interesting new family of molecules has gained strong interest recently, the major histocompatibility complex class I molecules (MHCI). They were initially discovered in a screen for activity-regulated molecules in the dLGN [106]. Subsequent experiments involved different immune molecules, such as CD3zeta and beta2-microglobulin, TAP1 [107], H2Db and H2K(b) [108], immune-like proteins such as the neuronal pentraxins [109] and immune molecules from the complement cascade such as C1q, C3 [110], and the complement receptor CR3 [111]. All these molecules have been involved in the refinement of eye-specific segregation and more specifically in synapse elimination. Interestingly, CR3 is expressed at the surface of microglia, thus eye-specific segregation in the dLGN could at least in part be mediated by phagocytosis of mislocalized projections by microglial cells [111]. Furthermore, secretion of TGFbeta by astrocytes induces C1q expression in RGCs followed by microglia-mediated synapse phagocytosis [112]. Thus, these complement molecules could act as "tags" to identify synapses that need to be eliminated by microglia. Importantly, this process is activity-dependent [111]. Recently, it has been demonstrated that astrocytes also are able to phagocyte retinal projections [113]. MEGF10 and MERTK are two important receptors for phagocytosis that are expressed in astrocytes. MEGF10 KO and MERTK KO mice show eye specific segregation defects and maintained multi-innervation of LGN neurons due to impairment of synapse elimination. Importantly, astrocyte-mediated synapse phagocytosis is activity-dependent [113].

Recently, some of the immune system molecules have been linked to alterations of neural plasticity. Mutants of the immune system molecules, H2Db, have impaired LTD after patterned stimulation mimicking endogenous retinal waves [114]. Along similar lines, it was shown that neuronal pentraxins 1 and 2 (NP1/2) are required for the normal development of AMPAR-mediated transmission and could convert silent synapses during eye-specific refinement [115]. The discovery of all these immune system molecules that are regulated by activity has gained more weight and has also implied new players such as microglia and astrocytes in synaptic refinement.

6. Specificity of ipsilateral projection

Many experiments highlight specific responses of the ipsilateral retinal projection to both guidance cues and activity. An interesting feature of the retinotopic organization is that ipsilateral axons are oriented with a different topography than the contralateral projection. Functional recordings in the ipsilateral SC show that ipsilateral inputs are oriented in a reverse manner [116] and anatomical tracing indicate that ventrotemporal RGCs project more caudally on the ipsilateral side compared to the contralateral side (Fig. 4B) [117]. This differential projection site of RGCs despite a similar topographic origin suggests that mechanisms controlling retinotopy differ in the contralateral and ipsilateral RGCs. Although both ipsilateral and contralateral axons are affected in ephrin mutants, their response to these guidance molecules could be interpreted differently for their final positioning. One interesting candidate is the molecule Ten_m3 which seems to affect specifically the

organization of ipsilateral axons [11], however the underlying mechanisms are still mysterious.

Second, the ipsilateral projection in the SC is more sensitive to activity changes. This is particularly clear for late activity changes: in various models, recovery of normal retinal activity rescues eye-specific segregation or retinotopic defects but not defects in the refinement of the ipsilateral projection [41,48,101]. Furthermore, in models with a smaller ipsilateral projection [19,118], eye-specific segregation is reduced suggesting a balance between ipsilateral and contralateral inputs for eye-specific segregation. In one of these models, EphB1-KO, the receptor guiding the retinal axons to the ipsilateral side is missing, causing the misrouted axons to project contralaterally: these axons still project to the normal "ipsilateral" domain but on the contralateral side suggesting that specific factors determine the position of the ipsilateral domain. Interestingly, the misrouted axons segregate from the rest of the contralateral projection and form an "ectopic patch" that is eliminated by epibatidine treatment and thus, is activity-dependent [19]. Other experiments showed that the refinement of ipsilateral axons seem to rely on different mechanisms than the Hebbian competition based rules because ipsilateral axons target the appropriate region and refine properly when glutamate release is perturbed [52]. In contrast, the contralateral axons that have normal glutamate release do not retract from the ipsilateral territory. These two experiments suggest that factors specific of the ipsilateral RGCs underlie synapse selection for eye-specific segregation as well as topographic refinement. Interesting candidates are molecules specifically affecting the ipsilateral projection such as teneurins [11,119] (Catherine Leamey, in this issue) or specifically expressed in ipsilateral RGCs such as the serotonin transporter [99]. More insight will likely come from studying the molecular factors specific to the ipsilateral RGCs and how they can be affected by activity changes.

7. Conclusions

More than twenty years after the discovery of spontaneous activity in the retina, we now clearly know that retinal waves are crucial for the refinement of visual maps and act in an instructive manner on eye-specific maps, even though the critical characteristics of retinal activity required for this process are still unclear. The use of new genetic models and of optogenetic tools to manipulate activity in addition to the characterization of retinal waves *in vivo* will certainly uncover which exact features of retinal activity are necessary. Some experiments also point toward an interdependence of visual maps. For instance, defects in eye-specific maps can secondarily affect retinotopic maps, rendering interpretations difficult and stressing the need to study in greater detail all the visual maps in models with perturbed activity. Also, activity acts on refinement through both Hebbian and non-Hebbian based rules and we now need to decipher the underlying cellular mechanisms. For instance, whether presynaptic release is required or not remains to be determined. It is also crucial to identify the downstream effectors of retinal activity. Interesting candidates such as adenylate cyclases, immune system molecules, retrograde signaling molecules have emerged in addition to factors such as 5-HT, that act to translate or to modulate the response to activity and thus contribute to the fine-tuning of the visual maps. In addition, an emerging field is the study of non-cell autonomous effects of axon circuit refinement, through synapse elimination by microglia or astrocytes. Deciphering the role of each of these factors and finding new molecular effectors needed for this conversion of activity into cellular effects such as axon branching or pruning will be an important direction in the future.

Acknowledgements

We thank past and present members of the laboratory for their contributions to the work reviewed here. Work in the laboratory of P. Gaspar related to the topic of this review was supported by INSERM, Retina France, and the Fondation pour la Recherche Médicale and is currently funded by INSERM, Université Pierre et Marie Curie, Fondation pour la Recherche Medicale. A. Assali was supported by a Ministry of Research doctoral fellowship and by a Retina France doctoral fellowship. A. Rebsam's work related to the topic of this review was funded by National Institutes of Health Grants EY012736 and EY015290, the Gatsby Initiative in Brain Circuitry and by postdoctoral fellowships from the Fondation pour la Recherche Medicale and the Human Frontier Science Program LT00399/2006-L, and is currently funded by the ANR #ANR-12-BSV4-0002, Genespoir and Fondation NRJ. The team is affiliated with the Paris School of Neuroscience (Ecole des Neurosciences de Paris-Ile-de-France) and the Bio-Psy Laboratory of Excellence.

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