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Wiring and Rewiring of the Retinogeniculate Synapse

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Abstract

The formation and refinement of synaptic circuits are areas of research that have fascinated neurobiologists for decades. A recurrent theme seen at many CNS synapses is that neuronal connections are at first imprecise, but refine and can be rearranged with time or with experience. Today, with the advent of new technologies to map and monitor neuronal circuits, it is worthwhile to revisit a powerful experimental model for examining the development and plasticity of synaptic circuits—the retinogeniculate synapse.

Introduction

The visual system is one of the best-understood sensory systems. It serves as an experimental model for sensory information processing as well as circuit development. Visual information encoded in the retina is transmitted via retinal ganglion cells (RGCs) to thalamic relay neurons in the dorsal lateral geniculate nucleus (LGN). Relay neurons, in turn, project to the primary visual cortex where higher order processing occurs. The retinogeniculate synapse is a powerful system for studying synaptic plasticity during development of the central nervous system (CNS). This simple circuit is accessible to both morphological and functional studies. Unlike most CNS synapses, where multiple developmental processes overlap over a short period of time, maturation of the retinogeniculate synapse extends over many weeks, facilitating the dissection of processes of axon targeting, of synapse formation, strengthening and elimination, and of experience-dependent plasticity.

The current understanding of synapse refinement at the retinogeniculate connection can be generalized to other areas in the CNS, including the cerebellum, brainstem and somatosensory system [1–3]. Development can be divided into three distinct phases: 1) axon targeting and rearrangement into proper lamina; 2) fine scale functional refinement, and 3) stabilization and maintenance of the refined circuitry (Figure 1). In this review, we draw from early studies in different species as well as recent ones from mice to review what is currently known about the mechanisms underlying the three phases and what questions remain unresolved.

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A Simple Circuit with Precise Connectivity

A striking feature of the retinogeniculate circuit is its anatomical and functional architecture. Early in development, RGC axons that reach the LGN must choose from numerous possible target neurons to form connections. The precise anatomical organization of these connections can be seen on multiple levels: (1) retinotopic mapping, whereby relative locations of RGCs in the retina are preserved in the LGN [4,5] (2) eye-specific segregation, by which projections from each eye terminate in non-overlapping territories within the LGN [5] (3) laminar specificity, in which different RGC types project to distinct cellular layers in the LGN [6]; and (4) subcellular specificity, whereby RGCs preferentially synapse onto proximal, rather than distal dendrites of LGN relay neurons [7]. Functionally, this precise connectivity is reflected in the receptive field properties of LGN cells. In the mature CNS, *in vivo* physiology from cat and other mammals has demonstrated that receptive fields of relay neurons are dominated by the inputs of one or two retinal ganglion cells; a single RGC drives nearly all the action potentials of the postsynaptic relay neuron [8,9].

A prime example of precise structural and functional organization is the laminar organization of inputs to the LGN. In many mammalian species, RGCs have been morphologically classified into 15~20 different subtypes, and each is thought to have distinct functional properties such as selectively responding to onset or offset of light (ON- or OFF-RGCs, respectively), or to a specific direction [6,10]. In addition to eye-specific layers, RGC subsets send axon terminals to distinct cellular layers in many species. The laminar organization that is a hallmark of monkey, cat, and ferret LGN was previously thought to be absent in mice, where such cellular layers are not readily discernable. However, recent identification of transgenic animals that each label a different RGC subset has revealed that subtypes of RGCs restrict their axon terminals to distinct and stereotyped laminae in the mouse LGN. Four such examples of transgenic subset lines are JAMB (labels OFF direction-selective RGCs) [11], CB2 (transient OFF- α RGCs) [12]; DRD4 (ON-OFF bistratified direction selective RGCs) [13], and BD (ON-OFF bistratified direction selective RGCs) [14] mice. Each labels a unique functional subset of RGCs whose axons terminate in restricted regions of the LGN (see Figure 2). It would be interesting to determine whether these laminae are mutually exclusive or overlap as they do in the mouse superior colliculus [15]. While the former would suggest segregation of parallel functional pathways, the latter scenario would open the possibility that certain RGC types converge onto single target neurons.

The remarkable specificity of the retinogeniculate synapse observed in the adult is not fully established in the young animal. How does this precise circuit develop? Recent work has harnessed the power of mouse genetics to address these questions. Despite the poor acuity of the mouse, features of its visual system have many similarities to that of primates and carnivores [16–18]. We review the molecular and activity-dependent mechanisms identified in these studies.

Distinct Phases of Development at the Retinogeniculate Synapse

Phase I: Axon Mapping and Rearrangement

Once RGC axons reach the LGN, large-scale structural changes occur, including retinotopic refinement and eye-specific segregation. Early in development, inputs from the two eyes target overlapping regions in the LGN. Gradually, inputs from the ipsi- or contra- lateral eye become segregated into separate layers through a process that involves the elimination of mistargeted synapses and the strengthening of correct ones [19,20]. In cat and monkey, eye-specific segregation is complete before birth, and in mice and ferrets, before eye-opening. Thus, the process of eye-specific segregation occurs prior to visual experience and is

mediated by spontaneous activity rather than vision. Several recent reviews extensively cover mechanisms of eye-specific segregation that will not be repeated here [5,21].

Phase II: Synapse Elimination and Strengthening

During the period when axons from different eyes overlap, functional synapses are present [19,22]. With the establishment of eye-specific layers synaptic refinement was generally thought to be complete. However, electrophysiological and EM studies have revealed that at this stage, synapses are still immature and evoke weak excitatory currents [23,24]. In mice, the majority of eye-specific segregation is complete by P8–10, immediately before eye-opening (P12–14) [25]. At this point, a single LGN cell receives 10 or more RGC inputs. Over the next three weeks, synapses strengthen 20-fold while the average number of RGC inputs (also referred to as single fiber inputs) onto a given relay neuron decreases to 1–3 [23,26,27]. Thus, synaptic refinement continues well after eye specific segregation is complete. The most robust functional refinement occurs around the time of eye opening. Between P8–16, more than half of the afferent inputs are functionally eliminated while the average strength of remaining inputs increases 8-fold. This period, which we define as the second phase of synapse remodeling, is dependent on spontaneous activity, not vision [26] (Figure 1). Spontaneous retinal activity during this period encompasses both retinal waves driven by glutamatergic transmission as well as spiking of individual RGCs. The detailed features of patterned activity that is important for this stage of synaptic refinement, and whether they are the same as those that drive the first phase of synapse remodeling remain unclear.

During the second phase of synapse refinement, the number of binocularly responsive LGN cells progressively decreases until eye-opening [27]. However, synaptic refinement at this stage does not solely represent remnant traces of eye-specific segregation. Even relay neurons located in regions of the LGN that become strongly monocular soon after birth (lateral LGN) are innervated by more than 10 RGCs just before eye-opening [23]. Temporally, this period corresponds to the sharpening of LGN receptive fields that occurs after eye opening [9,28]. Refinement could result from local competition between RGCs from a single eye, either between RGCs of the same, or different functional subtype. It is unknown how the RGC subtype-specific axon laminae (Figure 2) develop relative to one another, and whether they are still being refined during the second phase. Functional classification of RGCs is ambiguous at early stages, obscuring identities of RGC subtypes that drive an LGN cell. Newly available RGC subset markers will be invaluable in future studies to determine potential competition between RGC subtypes in synaptic maturation.

Phase III: Maintenance of Refined Circuitry and Vision-dependent Plasticity

Synaptic refinement continues between P16–32 in mice, albeit to a lesser extent than during the second developmental period. Single fiber strength increases an additional 2–3 fold and the average number of inputs innervating a relay neuron decreases by another 1–2 (Figure 3) [26]. The final stage of circuit refinement was thought to be independent of visual activity, as dark rearing animals from birth (chronic dark rearing) had no significant effect on receptive field refinement [29], pruning, or strengthening of synapses [26]. Surprisingly, dark rearing after a period of visual experience (late dark rearing) resulted in an increase in the number of inputs and weakening of RGC input strength (Figure 3). These findings revealed a previously unrecognized period of refinement that is sensitive to vision. Re-exposure to light after 7 days of deprivation resulted in rapid pruning and strengthening again, indicating that the changes in circuitry are reversible at this stage. Further investigation revealed that this plasticity is triggered by prior visual experience and occurs only during a discrete period of time, thus defining this phase as a critical period for the retinogeniculate synapse [30].

How can we reconcile the effects of late dark rearing with the fact that retinogeniculate synapses of chronically dark reared mice appear to refine normally? We propose a model in which spontaneous activity drives the majority of refinement of eye-specific segregation, retinotopy, and synaptic connections during the first two phases of development. By P20, a coarse approximation of the mature network is established and a single RGC makes connections to only a few of many potential postsynaptic partners. During the late phase of synapse remodeling, which is triggered by vision, the circuit can be further sculpted by visual experience. Based on visual experience during this time, an RGC can strengthen, weaken, or eliminate existing connections, or make new ones. Deprivation during this late phase of plasticity is an extreme and sudden change that strongly destabilizes the partially refined circuit, resulting in a robust change in synaptic strength and connectivity. In the case of mice dark reared from birth, this late phase of plasticity is never triggered, and thus the circuit remains in its default configuration.

Mechanisms Underlying Vision-Independent Plasticity

The mouse retinogeniculate connection has become a useful assay system for identifying mechanisms of synapse refinement. Several candidate molecules that play a role in eye-specific segregation have been identified from the screening of mutant mice for abnormalities. Mutations that disrupt spontaneous retinal activity, such as the nicotinic acetylcholine receptor $\beta 2$ subunit ($\beta 2$) null mice and *nob* mice show abnormalities in eye-specific segregation [31–33]. Disruption of axon guidance cues such as Wnt/ryk [34] and Eph/ephrin gradients also results in abnormal retinotopic map refinement in addition to disrupted segregation [4,35].

An unexpected theme that has emerged from the identification of a number of these molecules is their relationship to the immune system [36,37]. Recently, class I major histocompatibility complex (MHCI) molecules were found at a number of synapses in the CNS during development and adulthood, including in the retinogeniculate synapse [38–40]. Mutant mice with disrupted expression of MHC I molecules demonstrate defects in eye specific layer formation [38,41]. Electrophysiological studies of the role of MHCI show altered synaptic function although the specific defects differ depending on the particular synapse [41–44].

Another component of the immune system, the complement cascade, which is involved in marking foreign material for phagocytosis, have also been implicated in synapse elimination. Mice deficient in proteins in this cascade, C1q or C3, exhibit pronounced defects in eye-specific segregation [45]. Recordings from the retinogeniculate synapse at P30 show that, in addition to one strong input, multiple small weak inputs innervate an average relay neuron. These results suggest a working model in which complement proteins play a role in the proper removal of synapses that are destined for elimination [45].

Pentraxins are another family of molecules in the immune system that mark cells for phagocytosis and are known to bind C1q. Two pentraxin homologues found in the nervous system (NP1 and 2) are expressed in RGC axons during the period of synapse remodeling [46]. The NP1/2 knockout mouse exhibits delayed eye-specific segregation such that patterning of axonal projections is abnormal at P10, but not P30. Retinogeniculate synaptic recordings reveal substantially reduced AMPAR EPSCs, consistent with a defect in AMPAR recruitment into the synapse during the first phase of development (P6–9). However, by P17–20, single fiber AMPAR strength is normal in mutants, although relay neurons are innervated by an abnormally high number of RGC inputs [47]. It is not clear whether the disruption in innervation is corrected by P30, or whether eye specific

segregation is still abnormal at P17–20. These results suggest that the role of pentraxins in synaptic strengthening changes between the first and later phases of synapse remodeling.

Are the mechanisms that regulate the segregation of eye specific layers during the first phase of retinogeniculate synapse remodeling the same as those that drive synaptic refinement during the second phase of remodeling? Some mutants, such as C1q KO mice, exhibit disruption in both anatomy and function, indicating that the two phases share common mechanisms. However, not all mutants that exhibit disruption of eye-specific segregation have correlated abnormalities in retinogeniculate function. In the $\beta 2$ null mice that exhibit defects in eye specific segregation [31,32], and in ephrin triple knockout A2/A5/ $\beta 2$ null mice that have severe disruption of retinotopy and segregation (personal communication, D. Feldheim), *in vivo* recordings show remarkably little disruption in receptive field size and structure in the LGN [31,48]. Thus anatomical refinement can be dissociated from functional refinement, suggesting that regulatory mechanisms can differ between the two phases.

Synapse Strengthening and Elimination

Retinogeniculate recordings of NP1/2 and C1q KO mice show that disruption of synapse elimination can occur without affecting synapse strengthening. Over development, retinogeniculate strengthening occurs simultaneously with functional elimination of weaker afferent inputs. Hebbian mechanisms have been proposed to drive these changes [49]. In mice, bursts of presynaptic action potentials designed to mimic synchronous retinal wave activity can elicit a relatively small increase or decrease in synaptic strength, depending on whether they coincide with relay neuron bursting [50]. Studies in ferret, using paired stimuli, suggest that up to 2-fold potentiation in synaptic strength can be elicited by presynaptic activity [51]. This potentiation can account for the two-fold increase in quantal size that is found over development. However, an increase in quantal size accounts for just a fraction of the 20-fold increase in single fiber strength between P8 and P32. Since the probability of release does not significantly change over this developmental window, the number of release sites, or contacts between a single RGC and relay neuron, must increase dramatically [23].

Mechanisms Underlying Sensory Dependent Plasticity

Compared to the first two phases of synapse remodeling, little is known about the mechanisms underlying the recently identified visual experience-dependent retinogeniculate remodeling. Evidence for how sensory information can change synaptic connectivity was presented in a recent study that combined *in vitro* electrophysiology, EM immunolabeling and viral transfection of tagged AMPAR subunits [52]. Under basal visual activity, the GluR1 subunit is preferentially trafficked into postsynaptic densities (PSD) of retinogeniculate synapses but not corticothalamic synapses. GluR1 insertion into the PSD is regulated by calcium/calmodulin-dependent protein kinase II and small GTPase Ras activity, while removal of GluR1 is controlled by Rap kinase activity. Eye closure blocks GluR1 trafficking into the retinogeniculate PSD, thus reducing synaptic strength. It is not clear whether specific GluR1 trafficking occurs throughout development, or only during a specific period of time. However, it is likely that turnover of AMPAR subunits at retinogeniculate PSD must occur in order to remodel synaptic connections during the thalamic critical period.

Molecular mechanisms mediating the experience-dependent period of synapse remodeling should also be distinguishable from other developmental phases. MeCP2, a transcriptional regulator that has been associated with the neurodevelopmental disorder Rett Syndrome, is one such example. Analysis of retinogeniculate development in a *Mecp2* null mouse showed that synapse formation, strengthening and elimination during the first and second phases are not significantly different from WT littermates. However, synapses fail to strengthen further,

and the number of afferent inputs increases during the thalamic critical period, consistent with a role for MeCP2 in the modification of this circuit by sensory information [53].

Morphological Correlates to Synapse Remodeling

Much of our current understanding of structural synapse remodeling has been gained from studies in the peripheral nervous system. The neuromuscular junction (NMJ) is relatively large, accessible, and simple, facilitating *in vivo* imaging studies that have provided invaluable insight into the process of developmental synapse remodeling. Early in development, a single muscle fiber is transiently innervated by multiple motor neurons that are eventually eliminated until one input remains and strengthens. Retraction of axon branches is the structural correlate for this synapse elimination [54,55]. It is generally believed that a similar process occurs in the CNS, although detailed morphological analysis has been more challenging due to the significantly smaller size of the synapses, complex circuitry, and lack of accessibility to deep structures for *in vivo* imaging.

Similar to synapse remodeling at the NMJ, RGC projections are at first diffuse and undergo large-scale retraction to a focal region during retinotopic refinement in the mouse superior colliculus (SC) [56]. Recent studies indicate that a similar process occurs during laminar restriction of some RGCs in the SC. OFF- α RGC axon terminals initially span the full depth of the outer SC layer before becoming restricted to the deep retinorecipient layer [57]. Interestingly, the precise mechanisms of morphological development appear to be cell-type dependent [14].

On the postsynaptic side, morphological changes early in development involve the extension and retraction of dendritic branches of neurons that stabilize as synapses mature [58,59]. A recent study in the tadpole tectum, which is amenable to *in-vivo* time lapse imaging, showed that retinotectal synapses formed on stable dendrites are more mature and less dense than those on dynamic branches [60]. NMDAR blockade or visual deprivation delayed this synaptic maturation, consistent with activity-dependent mechanisms mediating synaptic refinement.

Large-scale structural changes are also believed to underlie the first phase of mammalian retinogeniculate synapse remodeling. However, classic studies of single axon morphology do not support a scenario in which a diffuse, complex axon arbor retracts to a focal target area during eye-specific segregation. Rather, at the earliest stages when axons between the two eyes are intermingled, individual axons hardly branch at all – axons exist as single twig-like structures with few short side branches [20]. The few side branches present in embryonic cat are even less evident in monkey [61]. As axons segregate into eye-specific regions, axon branches are removed, concurrent with robust elaboration of the axon arbor in the correct target areas (Figure 4). While much focus has been on the elimination of axon branches during eye-specific segregation, defects in this process may also be mediated by the excessive elaboration of mistargeted axons.

The anatomical basis of synapse remodeling during the later phases of plasticity remains unknown. Electrophysiological evidence indicates that during the second phase, synapses continue to be eliminated as receptive fields sharpen. However, compared to the time of eye opening, single RGC arbors in cat show further elaboration a few weeks later (Figure 4) [62]. There appears to be a discordance between the structural and functional changes that occur. However, it is important to note that “synapse elimination” in this context does not require a reduction in the number of synapses, but rather involves a decrease in the number of cells innervating a single postsynaptic cell. Synaptic strengthening is also occurring at this time, mediated by the addition of release sites. Thus, morphological changes underlying input elimination may be mediated by fine-scale axon remodeling, postsynaptic structural

changes reflected in dendritic morphology, or locally by biochemical or molecular changes at the release sites. Future studies are needed to shed light on these possibilities.

Conclusions

Much has been learned about the development of synaptic circuits in the mammalian CNS, yet many questions remain unanswered. While some CNS circuits form precisely without developmental refinement, others undergo large-scale changes over time. Is the act of refinement somehow advantageous to the mature circuit? Is the recruitment of afferent RGC inputs seen during late dark rearing due to reactivation of previously eliminated synapses, or formation of new pre- and post-synaptic partners? What are the morphological correlates to different phases of synapse remodeling? Can plasticity at the retinogeniculate synapse be reactivated? Answering these questions will provide further insight into how circuits form and how we can harness this plasticity to rewire circuits in the mature or diseased CNS. The recent development of circuit mapping tools such as trans-synaptic tracers, and high-throughput serial electron microscopy [63–65] will provide new approaches for answering these questions at the retinogeniculate synapse.

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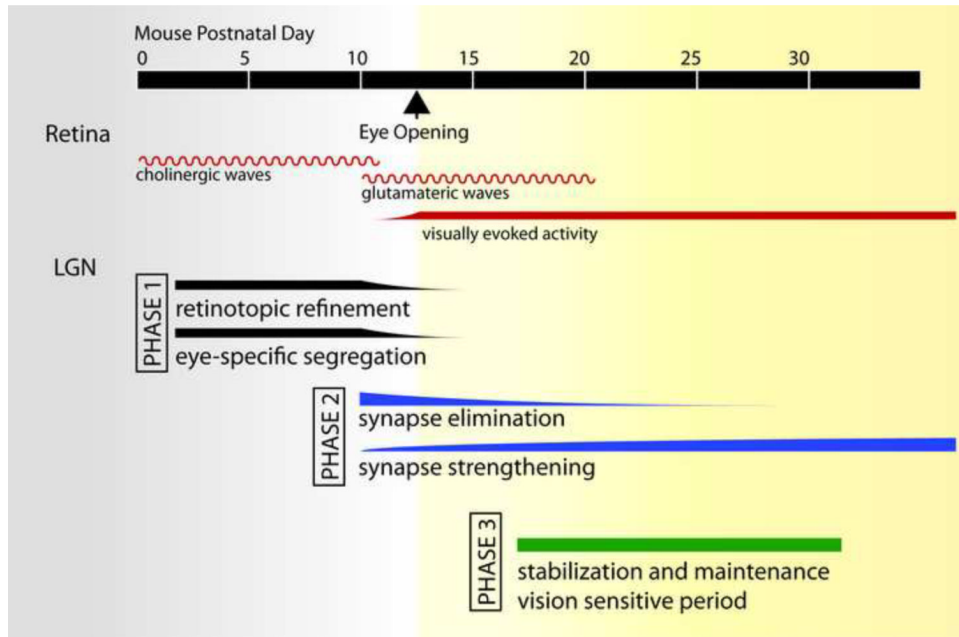


Figure 1. Developmental phases of retinogeniculate connectivity in mouse

In the retina (red lines), spontaneous activity in the form of cholinergic waves is followed by glutamatergic waves [5]. Eye-opening in mice occurs around postnatal day 12–14 (arrowhead). Visually evoked activity begins shortly before this, when light can be first detected through closed eyelids and persists throughout adulthood. Development of retinal connections to the dorsal lateral geniculate (LGN) can be divided into 3 phases. During phase I (black), axon refinement occurs during retinotopic refinement and eye-specific segregation. Throughout the second phase (blue), synaptic connections are further refined through continued elimination and strengthening of synapses. The third phase (green) involves the stabilization and maintenance of established connections. This period encompasses a period in which retinogeniculate connectivity can be influenced by visual experience.

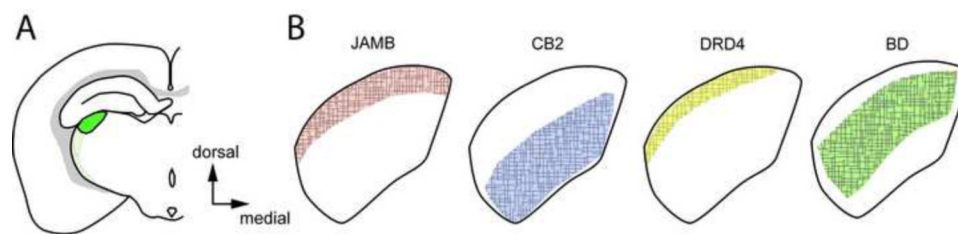


Figure 2. Laminar patterns of axon terminal projections in the mouse LGN

A. The location of the dorsal LGN in a mouse coronal section (green). **B.** Schematic representation of axon terminal zones in the LGN of transgenic mouse lines that selectively label functional subsets of RGCs including: JAMB, OFF-direction selective RGCs; CB2, transient OFF- α RGCs; DRD4-RGCs, ONOFF direction selective RGCs; and BD, ON-OFF direction selective RGCs [11–14]. Colored regions represent regions of the LGN that contained labeled axons of the different RGC subsets in the mature LGN. It is still unclear how these territories change over development. Identical contours of a coronal LGN section were drawn for simplicity and may represent different rostrocaudal sections.

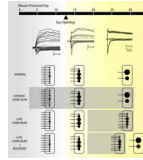
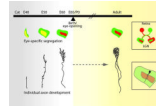


Figure 3.

Functional development of the mouse retinogeniculate synapse. (Top) Representative excitatory synaptic responses to incremental increases in optic nerve stimulation from P11, 17 and 28 mice [23]. Synaptic currents are recorded while alternating the holding potential between -70 mV (inward currents) and $+40$ mV (outward currents) to assess both AMPAR and NMDAR currents, respectively. (Bottom) Schematic representation of synaptic refinement is drawn to symbolize the experimental data for number of inputs and synaptic strength at different points in development [26,30]. Under normal conditions, synaptic strength increases by 20-fold and afferent inputs decrease from more than 10 down to just 1–3. An RGC input is symbolized by a horizontal line connected to a black circle; the size of the circle represents the relative strength of the input. Each black circle represents an axon making numerous contacts (release sites) with the postsynaptic neuron. Sensory deprivation by dark rearing animals from birth (chronic dark rear) shows no significant difference to normally reared mice. However, dark rearing after a period of visual experience (late dark rear), results in an increase in number of RGC inputs and weakening of established connections. During this period, these changes can be reversed when the animal is re-exposed to light (late dark rear + recovery).

**Figure 4.**

Structural development of retinal axon terminals in the LGN of the cat. We revisit these classic single-RGC morphology studies to compare the anatomical changes seen over development with the changes in retinogeniculate synaptic strength and innervation observed from mice. Similar single axon studies in mice are currently not available, thus comparisons are made relative to the time of completion of eye specific segregation and eye opening. (Top) Schematic representation of the progression of eye-specific segregation in the cat. Projections from one eye colored in red, the other in green (see top right box). Yellow region represents region of overlap between the two eyes (Bottom) Illustration of morphological changes of single RGC axon arbors described from classic studies in the cat. Bottom right box shows the location of the arbor within the LGN, Images of arbors adapted from [20] (embryonic (E) time points) and [62] (adult).