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Review

A Role for Correlated Spontaneous Activity in the Assembly of Neural Circuits

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Before the onset of sensory transduction, developing neural circuits spontaneously generate correlated activity in distinct spatial and temporal patterns. During this period of patterned activity, sensory maps develop and initial coarse connections are refined, which are critical steps in the establishment of adult neural circuits. Over the last decade, there has been substantial evidence that altering the pattern of spontaneous activity disrupts refinement, but the mechanistic understanding of this process remains incomplete. In this review, we discuss recent experimental and theoretical progress toward the process of activity-dependent refinement, focusing on circuits in the visual, auditory, and motor systems. Although many outstanding questions remain, the combination of several novel approaches has brought us closer to a comprehensive understanding of how complex neural circuits are established by patterned spontaneous activity during development.

Introduction

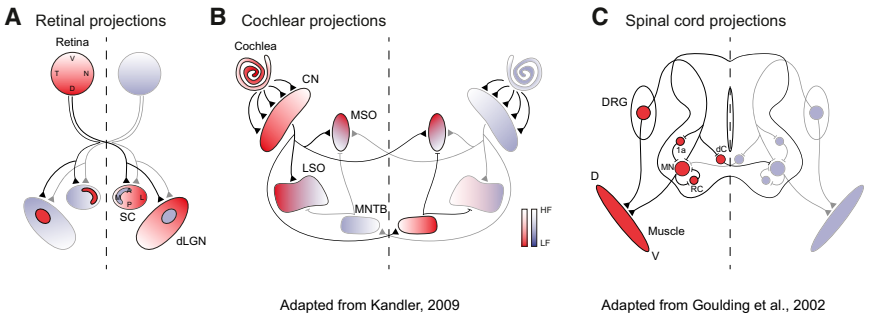
With almost one hundred billion neurons and one thousand as many synapses, the nervous system has a cumbersome task of ensuring that correct wiring is established during development. A major goal in developmental neurobiology is to elucidate the role that neural activity plays in this process. This review focuses on a particular period of development—after neuronal differentiation, migration, axon guidance, and dendrite extension, and before the onset of sensory experience—in which activity is generated spontaneously within the network and correlated among neighboring cells. During this developmental period, neural circuits undergo significant sculpting and refining of their connections, resulting in the formation of sensory maps and the establishment of precise local circuits (Katz and Shatz, 1996). Correlated spontaneous activity has been observed in several species, throughout the developing nervous system, including the retina, cochlea, spinal cord, cerebellum, hippocampus, and neocortex (Blankenship and Feller, 2010; Dehorter et al., 2012; Feldt et al., 2011; Moody and Bosma, 2005). This prevalence alone suggests that correlated spontaneous activity is an essential component of neural circuit maturation, and, as such, understanding the role of and mechanisms underlying correlated spontaneous activity has been a dynamic area of research over the past few decades.

Two major questions that remain in the field are, first, whether the endogenous patterns of activity are relevant for maturation of specific circuit features, and, second, what the learning rules that guide refinement are. It has been postulated that patterned spontaneous activity drives circuit refinement via learning rules that are consistent with Hebbian principles of plasticity, which state that the repeated and persistent stimulation of a postsynaptic cell by its presynaptic partner results in long-term strengthening of the synapse (long-term potentiation [LTP]) (Hebb, 1949), whereas weak or ineffective stimulation results in long-term weakening of the synapse (long-term depression [LTD]) (Katz and Shatz, 1996). Hence, the repeated stimulation provided by bursts of spontaneously active cells could provide the drive necessary for synaptic strengthening. Furthermore, the propagating nature and distinct spatial boundaries of spontaneous activity patterns would ensure that topographic maps are maintained across connected brain regions, because the connections between neighboring cells are strengthened, whereas those from more distant ones are lost (Eglen et al., 2003).

In this review, we summarize recent progress made toward answering these questions. We focus on the development of three circuits: retinofugal projections in the visual system, which is the most extensively studied system, cochlear projections to brainstem nuclei in the auditory system, and local motor networks in the spinal cord. In addition, we provide an overview of the theoretical frameworks that have contributed to our understanding of which spatial and temporal features of spontaneous activity are used for refinement of particular circuit features. By using optogenetic methods for precise control of firing patterns, elucidating the plasticity mechanisms that underlie map refinement, and creating models that allow for an interpretation of these results in the context of molecule-guided developmental processes, the field has made a significant step forward in the development of a comprehensive and mechanistic understanding of the role of spontaneous activity in circuit refinement.

Patterned Spontaneous Activity Guides Circuit Maturation

Following the first observations of correlated spontaneous activity (Galli and Maffei, 1988; Landmesser and O'Donovan, 1984; Lippe, 1994; Meister et al., 1991), the question of whether specific activity patterns are relevant to the formation and refinement



Adapted from Kandler, 2009

Adapted from Goulding et al., 2002

Figure 1. Retinal, Cochlear, and Spinal Cord Projections to Their Primary Targets

(A) Schematic representation of retinal ganglion cell projections to their primary targets: the dorsal lateral geniculate nucleus (dLGN) of the thalamus and the superior colliculus (SC). Red areas in the dLGN and SC correspond to projections from the left (red) eye; blue areas correspond to projections from the right (blue) eye. Shading represents retinotopy. V, ventral; D, dorsal; T, temporal; N, nasal; A, anterior; P, posterior; M, medial; L, lateral.

(B) Schematic representation of cochlear projections to primary brainstem targets: the cochlear nucleus (CN), the medial superior olive (MSO), the lateral superior olive (LSO), and the medial nucleus of the trapezoid body (MNTB). Red areas correspond to projections from the left (red) cochlea; blue areas correspond to projections from the right (blue) cochlea. Shading represents tonotopy. Both the LSO and MSO receive overlapping tonotopic maps originating from either cochlea. HF, high frequency; LF, low frequency. (Adapted from Kandler et al., 2009.)

(C) Schematic representation of some spinal cord cell types and their connections.

MN, motoneuron; DRG, dorsal root ganglia; RC, Renshaw cell; 1a, 1a inhibitory interneuron; dC, commissural interneurons; D, dorsal; V ventral. (Adapted from Goulding et al., 2002).

of nascent circuits emerged (Feller, 1999; O'Donovan, 1999). Since then, many lines of evidence point to patterned spontaneous activity playing a considerable role in the development of neural circuits. Spontaneous activity is conserved across species, throughout the nervous system, and is highly robust to perturbations, suggesting that developing networks have inherent redundancies to ensure that patterned activity is maintained (Blankenship and Feller, 2010; Turrigiano, 1999). In addition, many studies have shown that altering patterns of activity results in deficits in network refinement, suggesting that the patterns themselves contain information that guides such development (for visual system review, see Huberman et al., 2008). Here, we highlight recent in vivo studies that have shown that patterned spontaneous activity in the live animal has similar spatial and temporal properties to what has been described in vitro. In addition, we describe recent approaches that combine optogenetics and synaptic physiology to probe the cellular and synaptic basis of activity-dependent refinement driven by correlated spontaneous activity in the developing visual, auditory, and motor systems.

Sensory Map Formation in the Developing Visual System

Retinal Waves Coordinate Patterned Activity across Visual Areas

The visual system has been an ideal model to study how correlated spontaneous activity influences the development of neural circuits (reviewed in Huberman et al., 2008; Wong, 1999). Before the onset of vision, the immature retina generates spontaneous, periodic bursts of action potentials that sweep across retinal ganglion cells (RGCs) as a wave. Retinal waves have been observed experimentally in vitro and in vivo using a variety of techniques, including calcium imaging of RGCs, multielectrode array recordings, and paired patch-clamp recordings (reviewed in Torborg and Feller, 2005). In rodents, retinal waves are mediated by acetylcholine over the first 10 postnatal days of development, and by glutamate over the following 3–4 postnatal days. The endogenous patterns of cholinergic retinal waves are well characterized and have been described extensively (for review, see Ford and Feller, 2012). Briefly, waves occur at a frequency of approximately once per minute. A single wave propagates laterally across large fractions of retina and firing patterns are highly correlated among groups of RGCs that are within approximately 300 μm of one another. Typically, an RGC bursts for a duration of around 3 s during a given wave, at a firing rate of around 10 Hz. It has commonly been assumed that waves occur independently in left and right eyes; however, recent data have shown that a subset of waves is bilaterally coordinated between eyes (Ackman et al., 2012). Although the network underlying this coordinated activity remains unknown, observations of both descending retinopetal projections from higher brain areas (Gastinger et al., 2006) and retinoretinal projections between eyes (Ackman et al., 2012; Müller and Holländer, 1988) raises the possibility that it might be driven by common descending inputs or via interretinal connections.

RGCs project to the lateral geniculate nucleus (LGN) of the thalamus and the superior colliculus (SC), which, in turn, relay visual signals to the primary visual cortex (V1) (Figure 1A). A long-standing question has been whether retinal waves drive spontaneous activity in these downstream targets. Two approaches have been taken to answer this question. First, do the patterns of spontaneous activity in the LGN, SC, and V1 match what has been described in the retina? Second, does blocking inputs from the retina also block spontaneous activity of RGC targets in the brain?

Observing spontaneous activity in the visual system in vivo has been challenging because anesthetics such as isoflurane and urethane inhibit endogenous patterns of activity even at subsurgical doses, as had been demonstrated in cortex (Hanganu et al., 2006; Siegel et al., 2012). Several groups have recently studied endogenous patterns of spontaneous activity in vivo in unanesthetized animals, including zebrafish (Zhang et al., 2010), mouse (Ackman et al., 2012), rat (Colonnese and Khazipov, 2010), and human (Colonnese et al., 2010). In unanesthetized rodents, the temporal and spatial patterns of spontaneous activity in vivo was found to be similar to what was previously observed in vitro, suggesting that in vitro studies are representative of what occurs in the live animal.

Remarkably, a recent in vivo study showed that retinal waves drive correlated patterns of activity throughout the visual system, resulting in concurrent waves propagating across downstream

visual areas including the SC and V1 (Ackman et al., 2012). Spontaneous activity in the SC and V1 was found to be abolished (Colonnese and Khazipov, 2010) or greatly reduced (Ackman et al., 2012; Siegel et al., 2012) following enucleation or pharmacological block of retinal inputs. Similarly, correlated activity in the LGN was reduced following optic nerve transection (Weliky and Katz, 1999). These observations further support the conclusion that retinal waves coordinate patterned activity across developing visual brain areas. However, spontaneous activity in secondary visual cortex areas was found to be mostly uncorrelated with retinal waves, suggesting that activity in these areas is generated by a mechanism that is independent of retinal activity (Ackman et al., 2012).

Visual Maps Form in the SC and LGN over the Period of Retinal Waves

Over the period of cholinergic retinal waves, RGC projections to their primary targets, the dorsal LGN (dLGN) and SC, undergo significant sculpting and refinement. Recent reconstructions of single-axon arbors have provided a detailed description of refinement of mouse retinal projections (Dhande et al., 2011) that is similar to the classic work in cat (Sretavan and Shatz, 1986; Sretavan et al., 1988). This sculpting results in the formation of two sensory maps (refer to Figures 2A and 2B). One map reflects retinotopic location, where initially coarse axon terminals are refined to form precise terminals that map their location on the retina. Retinotopic map refinement occurs in both the SC and dLGN and is particularly prominent in the SC. The second map reflects inputs from left and right eyes, which project to both sides of the brain in mammals. In the dLGN, contralateral axons initially project over the entire region, whereas ipsilateral axons target a smaller patch that overlaps with the larger contralateral domain. During development, contralateral terminals are expelled from the ipsilateral patch and ipsilateral terminals refine and stabilize within the patch. Similar eye-specific segregation is observed in the anteromedial region of the SC. This region initially receives binocular input, and, over the course of development, ipsilateral axons segregate into small patches of ipsilateral-only projecting neurons. These two sensory maps are referred to as retinotopy and eye-specific segregation, respectively.

Experimentally, retinotopy is assayed using a focal DiI injection into a given location on the retina, which results in a labeled spot in the SC. The extent of retinotopic refinement is quantified by the size of the DiI-labeled target zone in the SC (for detailed methods, refer to Chandrasekaran et al., 2005). Eye-specific segregation is assayed using vitreal injection of cholera toxin fused to a fluorescent dye, which bulk labels most RGCs and their axon projections. By using two different fluorophores for either eye, typically one red and one green, the extent of segregation is quantified by measuring the fraction of the LGN that contains red-only or green-only fluorescence (segregated regions), compared to the fraction that contains an overlap of both red and green fluorescence (unsegregated region) (for more detail on quantification techniques, refer to Huberman et al., 2003; Stellwagen and Shatz, 2002; Torborg et al., 2004).

In addition to anatomical measures, physiological recordings of neurons in the SC and dLGN have been made to assess the formation of functional maps. Retinotopy has been assayed in vivo by measuring the receptive fields of SC neurons at the time of eye opening (Chandrasekaran et al., 2005). These measurements showed that the receptive fields are circular and compact, covering an area comparable to the size of retinocollicular projections as assayed using retinal DiI injections. In addition, the number of RGC inputs onto either collicular (Furman and Crair, 2012) or geniculate (Hooks and Chen, 2006) neurons has been quantified in vitro my comparing the saturated synaptic response of a neuron induced by high-intensity stimulation to the single-fiber response induced by minimal stimulation. Eye-specific segregation has been assayed in vivo by measuring single-cell responses in the dLGN to visual stimulation at eye opening (Grubb et al., 2003). These recordings showed that geniculate neurons were driven by monocular stimulation both within the contralateral region and the ipsilateral patch. Furthermore, in vitro recordings of dLGN neurons have shown that geniculate neurons initially receive binocular inputs, with one eye exerting a stronger synaptic drive onto a given neuron than the other eye, and that inputs from the weaker eye are eliminated as segregation proceeds (reviewed in Guido, 2008; Huberman, 2007). Together, these observations are consistent with anatomical changes occurring in the SC and dLGN over the same developmental period. Physiological measurements provide additional information over anatomical measurements, allowing researchers to put constraints on the underlying cellular and molecular mechanisms of map formation. For example, they allow researchers to test whether particular types of plasticity mechanisms, such as LTP or LTD, exist at target synapses (Butts et al., 2007; Ziburkus et al., 2009).

Endogenous Patterns of Retinal Waves Instruct Specific Aspects of Visual Map Formation

Although the initial formation of retinotopic and eye-specific segregation maps is thought to be largely laid out by molecular cues (Feldheim and O'Leary, 2010; Triplett and Feldheim, 2012), their subsequent refinement is considered to be activity dependent (Cline, 2003; Goodman and Shatz, 1993; Huberman et al., 2008). In particular, the endogenous patterns of retinal waves have been implicated in the refinement of retinotopic and eye-specific maps. By conveying information about neighboring cells to higher brain regions, the restricted propagating spatial structure of waves could provide an instructive cue for retinotopy, whereas the independent timing of inputs from left and right eyes could provide an instructive cue for eye-specific segregation via activity-dependent competition.

Classically, this hypothesis has been tested using pharmacological manipulations and transgenic mice that alter patterns of retinal activity (summarized in Table 1). The strongest and best-characterized phenotype has been a mouse model that lacks the β2 subunit of the nicotinic acetylcholine receptor (β2-nAChR KO) and as such lacks normal cholinergic waves (Bansal et al., 2000; McLaughlin et al., 2003; Rossi et al., 2001). β2-nAChR KO mice exhibit gap junction-mediated correlated firing patterns with spatiotemporal properties that are distinct from cholinergic waves (Kirkby and Feller, 2013; Stafford et al., 2009; Sun et al., 2008a; Torborg et al., 2005); gap junction waves in β2-nAChR KO mice are larger and faster than cholinergic waves, burst durations are shorter, firing rates during a burst

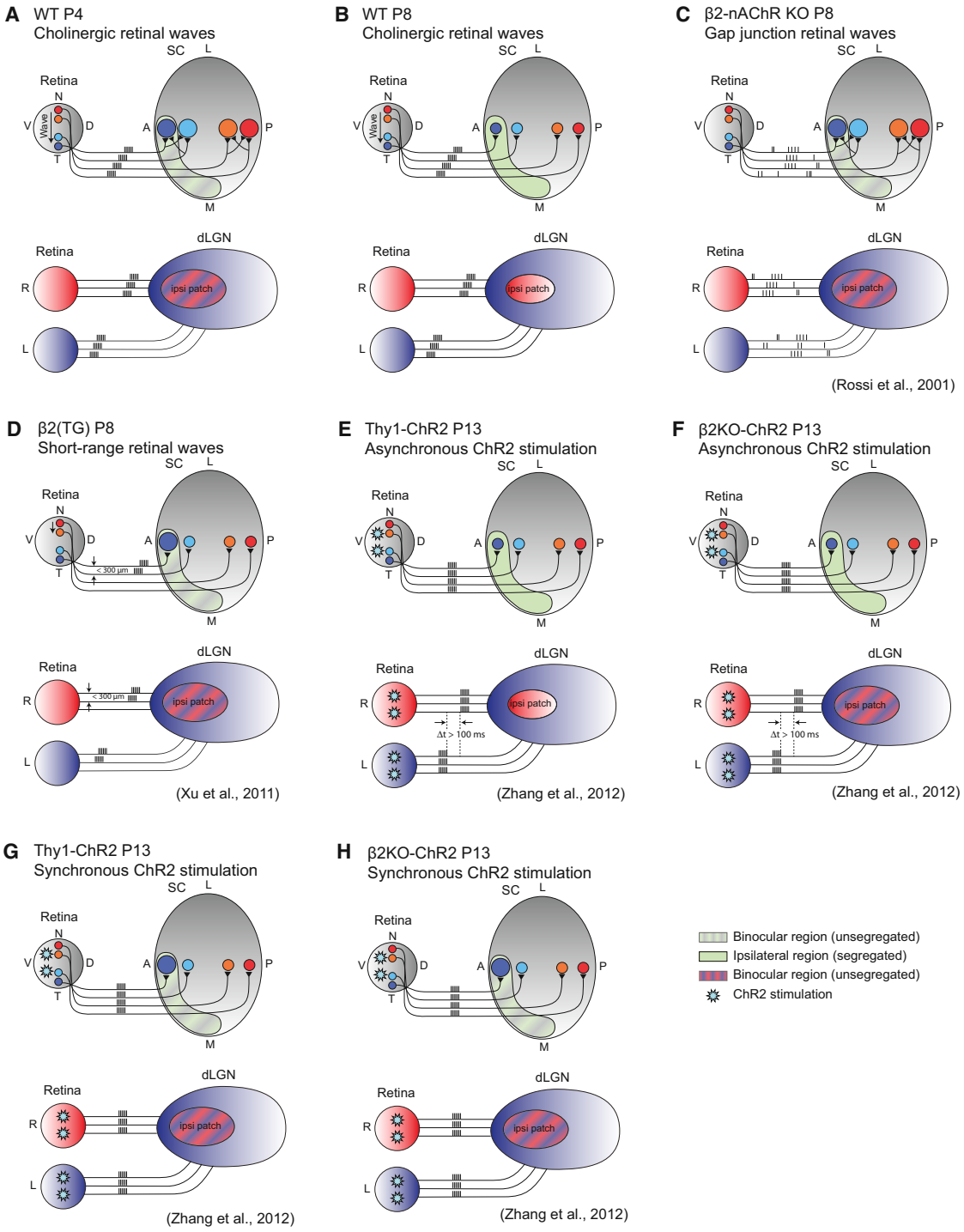


Figure 2. Retinotopic Map Formation and Eye-Specific Segregation under Normal and Disrupted Spontaneous Retinal Activity Patterns
Schematic representations of retinotopic map formation in the SC and eye-specific segregation in the dLGN during normal development (A and B) and as a result of experiments that alter the spatial and temporal pattern of afferent RGC activity (C—H), as described in the text. Note that although the SC schematic is used to represent retinotopic mapping and the dLGN schematic to represent eye-specific segregation mapping, both maps refine in the two visual regions. Large and small circles depicted in the SC correspond to the termination zone size of RGC axons, shading corresponds to retinotopy, and striped regions correspond to unsegregated inputs from left and right eyes. SC, superior colliculus; dLGN, dorsal lateral geniculate nucleus; V, ventral; D, dorsal; T, temporal; N, nasal; A, anterior; P, posterior; M, medial; L, lateral; R, right eye; L, left eye; ChR2, channelrhodopsin-2.

are lower, and waves occur less frequently. In addition, β2-nAChR KO mice exhibit high levels of uncorrelated firing in between waves (Stafford et al., 2009; Torborg et al., 2004). β2-nAChR KO mice show striking defects in both retinotopy and eye-specific segregation (reviewed in Huberman et al., 2008) (Figure 2C). This led to the conclusion that normal patterns of retinal waves are required for normal map formation. However, the inability to distinguish between the effect of disrupting wave patterns with the effect of disrupting overall firing patterns led to different interpretations of how and whether patterned activity contributes to sensory map formation (reviewed in Chalupa, 2009; Feller, 2009).

More recently, researchers have used sophisticated transgenic and optogenetic tools to determine whether the precise pattern of spontaneous activity is important for map development. By generating a transgenic mouse in which expression of β2-containing nAChRs is restricted to the ganglion cell layer of the retina (β2(TG)), researchers developed a manipulation that independently affected refinement of retinotopic maps and eye-specific segregation (Xu et al., 2011), in contrast to the more extensive full-body β2-nAChR KO, which shows defects in both maps. β2(TG) mice exhibit "truncated" cholinergic waves, which propagate over shorter ranges compared to normal cholinergic waves, but otherwise show single-neuron RGC firing activity that is indistinguishable from wild-type (WT) mice. In β2(TG) mice, the retinotopy defects seen in β2-nAChR KO mice were rescued in both the SC and dLGN, indicating that correlated firing among small groups of neighboring cells can drive axon refinement (Figure 2D). However, the truncated wave pattern did not rescue eye-specific segregation defects seen in β2-nAChR KO mice in either the SC or the dLGN, suggesting that long-range wave propagation is necessary for normal segregation patterns.

Optogenetic techniques have provided a more systematic approach to test whether the relative timing of inputs from left and right eyes provides an instructive cue for the formation of eye-specific segregation. By expressing and stimulating the light-gated cation channel channelrhodopsin-2 (ChR2) in approximately 20% of RGCs distributed uniformly across the retina, researchers were able to reliably manipulate the timing of retinal inputs to its primary targets in the brain (Zhang et al., 2012). In WT mice, asynchronous stimulation of left and right eyes resulted in segregation patterns in the SC and dLGN that were similar to control conditions (Figure 2E). In addition, this stimulation protocol somewhat rescued eye-specific segregation defects seen in the SC of β2-nAChR KO mice but did not alter segregation patterns in the dLGN, indicating that optogenetic stimulation was less effective in influencing eye-specific segregation in the dLGN compared to the SC (Figure 2F). In contrast, synchronous stimulation of both eyes in WT mice disrupted eye-specific segregation in both the SC and dLGN, for both WT and β2-nAChR KO mice (Figures 2G and 2H). The extent of segregation improved with increasing asynchrony of left and right eye stimulation. Furthermore, segregation was sensitive to bursting of RGCs with timescales on the order of 100 ms, rather than individual spikes, suggesting that burst timing rather than spike timing provides an instructive signal for segregation. This is expected, because the weak and diffuse connections of presynaptic cells during development (Chen and Regehr, 2000; Guido, 2008; Ziburkus et al., 2009) likely renders them impervious to plasticity on the fast timescales of individual spikes, which occur on the order of 10 ms (Butts and Kanold, 2010).

Surprisingly, the uniform stimulation protocol led to an improvement in retinotopy for some axons in WT mice, and a marked improvement in retinotopy for β2-nAChR KO mice, suggesting that the high frequency of bursting activity may be more important for retinotopic refinement than the specific spatial pattern of activity (Zhang et al., 2012) (Figures 2E–2H). However, because ChR2 was expressed only in a small subset of RGCs (approximately 20%), the authors proposed that sparse activation of RGCs during stimulation could produce inhomogeneous spatial patterns that drive retinotopy.

Together, these studies suggest that the endogenous burst-like and highly correlated pattern of retinal waves is indeed suited to refinement of these two visual sensory maps. With the further development of better optogenetic and transgenic techniques, researchers will be able to mimic and manipulate natural patterns of activity in ever more systematic ways, allowing us to unequivocally assess which spatial and temporal features of patterned retinal activity are used for refinement of which sensory map features.

Sensory Map Formation in the Developing Auditory System

Similar to visual system development, before the onset of hearing in the developing auditory system, the immature cochlea generates spontaneous activity that sweeps across inner hair cells (IHCs) and spiral ganglion neurons (SGNs) (for review, see Kandler et al., 2009). Rhythmic bursts of action potentials in IHCs and SGNs occur at a periodicity of approximately three per minute and are correlated among neighboring groups of cells. These events are triggered and synchronized by ATP release from supporting cells (Tritsch et al., 2007; Tritsch and Bergles, 2010), although spike generation in IHCs may be intrinsic to the cell itself (Johnson et al., 2011). ATP-triggered IHC depolarizations result in Ca^{2+} spikes that drive discrete bursts of action potentials in SGNs (Tritsch et al., 2010). Furthermore, the frequency and pattern of IHC spiking activity varies along the length of the cochlea, where basal cells, which in the adult brain are tuned to high frequencies, show more sustained firing and higher mean firing rates compared to apical cells, which show bursting activity and lower mean firing rates (Johnson et al., 2011, 2012).

SGN axons target the cochlear nucleus (CN) in the brain via the auditory nerve (Figure 1B). These projections are tonotopically mapped, resulting in a spatial separation of axon terminals from cochlear neurons that are tuned to high-frequency sounds to those that are tuned to low-frequency sounds. This tonotopy is further mapped onto three auditory nuclei downstream from the CN: the medial nucleus of the trapezoid body (MNTB), the lateral superior olive (LSO), and the medial superior olive (MSO). CN axons project to the contralateral MNTB, the ipsilateral LSO, and to both the ipsi- and contralateral MSO. Each MNTB, in turn, projects to its ipsilateral LSO and MSO. As such, both the LSO and MSO receive tonotopic input from both cochleae—excitatory input via the CN and inhibitory input via the MNTB.

Table 1. Summary of Manipulations to Study Retinofugal Map Formation and Refinement

Manipulation	Retinal Activity	Retinotopic Refinement	Eye-Specific Segregation
Manipulations primarily affecting retinal activity			
Prenatal TTX application in cat (Shatz and Stryker, 1988)	Action potentials blocked	Unknown	No segregation
Postnatal introacular TTX injection in ferret (Cook et al., 1999)	Action potentials blocked	Unknown	Normal segregation
Binocular epibatadine (nAChR antagonist) injections in ferret and mouse (Cang et al., 2005; Huberman et al., 2002, 2003; Penn et al., 1998; Rossi et al., 2001; Sun et al., 2008b)	Retinal waves blocked in both eyes	Reduced refinement	No segregation
Monocular epibatadine (nAChR antagonist) injections in ferret (Penn et al., 1998)	Retinal waves blocked in one eye	Reduced refinement	Reduced segregation of inputs combined with increase in axonal territory of active eye
Binocular cpt-cAMP injections (Stellwagen and Shatz, 2002)	Increase in wave frequency in both eyes	Unknown	Normal segregation
Monocular cpt-cAMP injection (Stellwagen and Shatz, 2002)	Increase in wave frequency in one eye	Unknown	Reduced segregation of inputs combined with increase in axonal territory of more active eye
Binocular ChAT immunotoxin injection (kills 80%–95% of SACs) (Huberman et al., 2003; Speer et al., 2011)	Retinal waves with reduced nearest neighbor correlations	Unknown	Normal
β2-nAChR KO mouse (lacks β2-subunit of nAChRs) (Grubb et al., 2003; McLaughlin et al., 2003; Muir-Robinson et al., 2002; Rossi et al., 2001)	Gap junction-mediated retinal waves with reduced nearest neighbor correlations; increased uncorrelated firing between waves	Reduced refinement	Reduced segregation
Rescue of β2-containing nAChRs in RGCs of β2-nAChR KO mouse (Xu et al., 2011)	Small-range cholinergic retinal waves	Normal refinement	Reduced segregation
Cx36 KO and Cx45 KO mice (lack gap junction proteins Cx36 and/or Cx45) (Blankenship et al., 2011; Torborg et al., 2005)	Retinal waves with increased interwave firing	Unknown	Single KO, normal segregation; Cx36-Cx45 double KO, reduced segregation
No b-wave mouse (Demas et al., 2006)	Retinal waves with abnormal retinal activity after P14	Unknown	Normal segregation at eye opening; segregation degrades after eye opening
Opn4 KO mouse (lacks photopigment melanopsin) (Renna et al., 2011)	Retinal waves with shorter burst duration during waves compared to WT in mice reared in constant light	Unknown	Reduced segregation
Manipulations affecting either retinofugal synapses or the targeting of retinal projections			
AC1 KO mouse (lacks the calcium-dependent adenylate cyclase 1) (Dhande et al., 2012; Plas et al., 2004)	Normal retinal waves	Reduced refinement	Reduced segregation
MAOA KO mouse (lacks monoamine oxidase A resulting in excess serotonin) (Upton et al., 1999, 2002)	Unknown	Reduced refinement	Reduced segregation
CREB KO mouse (reduced CREB expression) (Pham et al., 2001)	Unknown	Unknown	Reduced segregation
Monocular antisense BDNF injections (blocks BDNF mRNA in the retina) (Menna et al., 2003)	Unknown	Unknown	Reduced axonal territory of treated eye
Binocular U0126 or PD98059 injections (reduces ERK activation) (Naska et al., 2004)	Unknown	Unknown	Reduced segregation

(*Continued on next page*)

Table 1. *Continued*

Manipulation	Retinal Activity	Retinotopic Refinement	Eye-Specific Segregation
Altered ephrin expression/signaling (Cang et al., 2008; Huberman et al., 2005; Pfeiffenberger et al., 2005, 2006)	Normal	Disrupted targeting but normal refinement	Reduced segregation
β3 KO mouse (lacks the β3 subunit of the L-type calcium channel) (Guido, 2008)	Unknown	Unknown	Reduced segregation
Knockout of molecules associated with MHC1 signaling (Datwani et al., 2009; Huh et al., 2000; Syken et al., 2006)	Normal retinal waves	Unknown	Reduced segregation
NP1/2 KO mouse (lacks neuronal pentraxins NP1/2) (Bjartmar et al., 2006; Koch and Ullian, 2010)	Normal retinal waves	Unknown	Reduced segregation
CD3zeta KO mouse (lacks the immune protein CD3zeta) (Xu et al., 2010)	Altered glutamatergic waves	Unknown	Reduced segregation
C1q KO mouse (lack complement proteins C1q) (Stevens et al., 2007)	Normal retinal waves	Unknown	Reduced segregation
CR3 KO and C3 KO mice (lack microglia specific complement receptors) (Schafer et al., 2012)	Normal retinal waves	Unknown	Reduced segregation
Ten-m3 KO and Ten-m2 KO mice (lack members of teneurin family of glycoproteins) (Leamey et al., 2007; Young et al., 2013)	Normal retinal waves	Altered ipsilateral mapping	Reduced segregation
Intracranial infusion of FK506 (calcineurin blocking enzyme) in ferret (Leamey et al., 2003)	Unknown	Unknown	Normal eye specific segregation; reduced ON/OFF segregation[a]
MeCP2 KO (lacks the transcriptional regulator MeCP2) (Noutel et al., 2011)	Normal retinal waves	Unknown	Reduced segregation
DSCAM mutants (various mouse models of Down syndrome) (Blank et al., 2011)	Normal retinal waves	Unknown	Reduced segregation
Phr1 KO (lacks a protein that is a regulator of synapse formation and axon guidance) (Culican et al., 2009)	Normal retinal waves	Unknown	Reduced segregation

Summary of manipulations affecting retinal activity, retinofugal synapses, and targeting of retinal projections on retinotopic map refinement of retinocollicular projections and eye-specific segregation of retinogeniculate projections.
[a]ON/OFF segregation is not discussed in this review.

In these nuclei, the tonotopic maps from either cochlea are precisely aligned, such that single LSO or MSO neurons are excited and inhibited by the same frequency of sound (Kandler et al., 2009).

Because auditory circuits are tonotopically assembled early in development, it was originally thought that tonotopic map formation was hardwired by molecular cues (Gurung and Fritzsch, 2004; Kandler and Friauf, 1993; Rubel and Fritzsch, 2002). However, there is growing evidence that tonotopic precision in auditory nuclei increases during development (Kandler et al., 2009). In particular, the CN shows refinement of SGN axon terminals, and the LSO and MSO show significant synaptic reorganization, which results in the precise alignment of tonotopic maps from either cochlea. Whether correlated spontaneous activity in the immature cochlea drives this refinement and what the underlying cellular mechanisms are remain to be determined. One possibility is that tonotopy is relayed to auditory nuclei by the correlated activity of small groups of neighboring (tonotopically similar) cells, compared to the uncorrelated activity of nonneighboring (tonotopically distinct) cells. This hypothesis is supported by the finding that activity patterns initiated in the cochlea propagate to auditory nuclei in the brain, including the MNTB and the central nucleus of the inferior colliculus (CIC) (Tritsch et al., 2010). Moreover, the observation of spatially inhomogeneous firing patterns between basal and apical hair cells raises the intriguing possibility that the temporal structure of IHC firing rates contains relevant instruction for guiding tonotopy and for establishing precise frequency tuning of downstream auditory neurons. Further support for this model comes from recent evidence that shows that synaptic release at IHC terminals is dependent on the pattern of action potential activity (Johnson et al., 2013).

With increased understanding of the cellular mechanisms underlying the generation of correlated spontaneous activity in IHCs, combined with directed transgenic and optogenetic

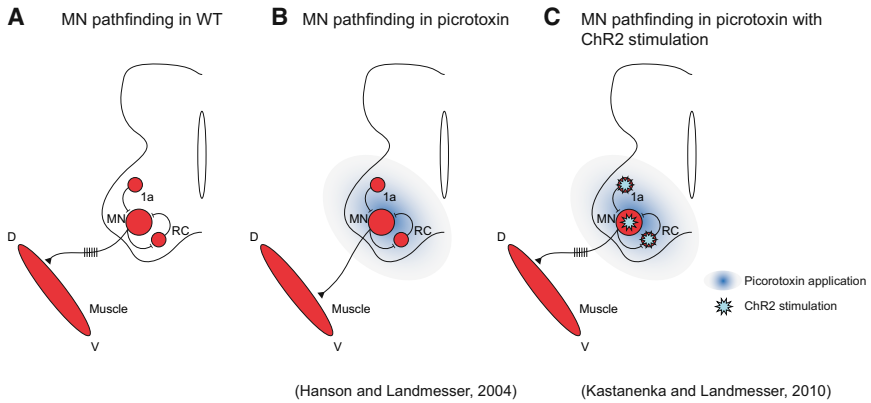


Figure 3. Motoneuron Pathfinding in the Developing Spinal Cord under Normal and Disrupted Activity Patterns

Schematic representation of motoneuron pathfinding in the developing spinal cord during normal development (A), in the presence of the GABA-A antagonist picrotoxin (B), and in the combination of picrotoxin and ChR2 stimulation (C). V, ventral; D, dorsal; MN, motoneuron; RC, Renshaw cell; 1a, 1a inhibitory interneuron; ChR2, channelrhodopsin-2.

manipulations, researchers will be able to alter IHC activity in controlled ways and test the effects of altered firing patterns on tonotopic refinement in auditory nuclei.

Circuit Formation in the Developing Motor System

Before adult synaptic connectivity is established, neurons in the developing spinal cord exhibit periodic bursts of spontaneous activity that are correlated among neighboring cells and propagate down the length of spinal cord segments (O'Donovan, 1999) (Figure 1C). During early stages of development, this spontaneous network activity (SNA) is driven primarily by depolarizing GABA and glycine, whereas at later stages it is driven primarily by glutamate and acetylcholine (Momose-Sato and Sato, 2013). Mature connectivity is established once GABA signaling becomes inhibitory. SNA events occur at a frequency of approximately once per 1–3 min and occur synchronously between left and right sides of the spinal cord. SNA should not be confused with brainstem-driven correlated activity that occurs during later postnatal developmental stages, before central pattern generator circuits are functional (Nishimaru and Kudo, 2000). This evoked, correlated activity alternates between left and right sides of the spinal cord and is thought to contribute to the development of locomotion, which shows similar alternating activity patterns.

Correlated spontaneous depolarizations of motoneurons are thought to drive early spontaneous limb movements of developing embryos (Blumberg et al., 2013; Crisp et al., 2011, 2008), a phenomenon that was first observed several decades ago (Hamburger and Balaban, 1963; Ripley and Provine, 1972). In addition, SNA has been implicated in several aspects of spinal cord circuit development, including axon pathfinding, changes in connectivity, cellular excitability, maturation of synaptic strength, and possibly functional circuit refinement (reviewed in Wenner, 2012). For example, the developing chick embryo shows reorganization of an inhibitory interneuron spinal cord circuit over the period of spontaneous activity, where GABAergic projections undergo functional refinement of initially coarse synaptic projections (Xu et al., 2007). However, unlike sensory systems, motor systems are not organized in spatial, sensory maps. Thus, whether the precise patterns of spontaneous activity are necessary for the correct development of spinal circuits, in an analogous process to the refinement of sensory maps, remains an open question.

Recently, optogenetic tools have been used to address this question. One approach has been to use ChR2 to alter the firing properties of spinal cord motor neurons (Crisp et al., 2011; Kastanenka and Landmesser, 2010). For example, in wild-type *Drosophila*, spontaneous motor neuron activity first drives disorganized muscular contractions at 17 hr postfertilization (hpf). Contractions rapidly become coordinated, with the first peristaltic wave—a sequential activation of muscle segments from posterior to anterior—occurring approximately 1 hr later, at 18.25 hpf. ChR2 was expressed in all neurons and used to change the pattern of activity. Stimulating all neurons at 1 Hz from 17–18 hpf caused a delay of up to 90 min in the onset of mature peristaltic movement, indicating that the endogenous frequency of spontaneous neuronal activity is required for the normal maturation of coordinated motor function (Crisp et al., 2011).

In another example, the frequency of spontaneous network events was found to be required for normal motoneuron axon guidance in the developing chick (Kastanenka and Landmesser, 2010). Blocking or slowing the frequency of spontaneous events in the developing spinal cord using the GABA-A receptor antagonist picrotoxin results in marked motoneuron axon pathfinding errors in the limb (Hanson and Landmesser, 2004). However, normal pathfinding was rescued when endogenous patterns of neural activity were restored using ChR2 activation in the presence of picrotoxin (Kastanenka and Landmesser, 2010) (Figure 3). These observations suggest that axon pathfinding in developing spinal circuits does not require GABA-A receptor activation in particular, but rather depends on specific patterns of activity.

An alternative optogenetic approach has been to use the light-gated inhibitory chloride pump Halorhodopsin (NpHR) to chronically inhibit neuronal activity, as has been recently done in zebrafish (Warp et al., 2012). Spontaneous network activity has been well characterized in the developing zebrafish spinal cord (Brustein et al., 2003). Briefly, activity is initiated by a cluster of interneurons that exhibit pacemaker-like activity (Tong and McDearmid, 2012). Activity of ipsilateral motoneurons becomes increasingly synchronous from 18 to 20 hpf. By 20 hpf, synchronous bursting alternates between the ipsilateral and contralateral spinal cord (Saint-Amant and Drapeau, 2001; Warp et al., 2012). Chronic inhibition of motoneuron activity from 18 to 19 hpf using NpHR stimulation resulted in a reduction of correlated activity among ipsilateral neurons, up to 22 hpf (Warp et al., 2012). Furthermore, neurons located at the midline of the spinal cord

showed prolonged immature spontaneous transients, suggesting that correlated spontaneous activity is essential for integration of new cells into the motor circuit.

Together, these reports suggest that early patterned spontaneous activity in the spinal cord plays an instructive role in the formation of spinal cord circuits, and, in particular, that axon pathfinding and neuron integration into developing circuits depend on endogenous patterns of activity in spinal cord neurons.

Learning Rules of Activity-Dependent Circuit Maturation

Although the refinement and maturation of sensory maps and motor circuits are considered to be activity dependent, the learning rules that drive circuit refinement remain largely unknown. Based on studies in frogs and fish, the prevailing model of activity-dependent circuit refinement in the developing visual system is Hebbian based, in which connections between pre- and postsynaptic cells that undergo coincident activation are strengthened and stabilized, whereas those that do not are weakened and lost (Ruthazer and Cline, 2004). In these species, vision matures early, and there is no evidence of correlated spontaneous activity (Demas et al., 2012). The same learning rules have been applied in mammals for how the repeated and persistent stimulation of a postsynaptic cell during periods of correlated spontaneous activity might drive similar refinement processes (for reviews, see Butts, 2002; Huberman et al., 2008; Katz and Shatz, 1996). However, many studies that have addressed this question alter pre- and postsynaptic neural activity in conjunction with each other. Therefore, it remains unknown whether non-Hebbian mechanisms—which require activation of either a pre- or a postsynaptic cell but not coincident activation of both—contribute to circuit refinement during development. Below, we discuss recent progress made toward this question from studies in the developing visual system. In addition, we summarize recent insights gained from computer models into the learning rules that underlie circuit refinement.

Activity-Dependent Competition in the Developing Visual System

Eye-Specific Segregation in the dLGN Combines Hebbian and Non-Hebbian Instruction

Eye-specific segregation in the dLGN has long been studied as an example of activity-dependent competition (for reviews, see Huberman et al., 2008; Katz and Shatz, 1996). In the classic model, the formation of eye-specific regions depends on a Hebbian-based learning rule, in which dominant inputs become stronger at the expense of weaker ones. In particular, ipsilateral inputs are thought to drive contralateral inputs out of the ipsilateral domain (reviewed in Torborg and Feller, 2005). Several studies that alter the relative activity of RGCs from either eye support this model. For example, blocking or increasing the frequency of waves in one eye results in the less active eye losing axonal territory to the more active eye. In contrast, increasing activity equally in both eyes has no effect on segregation (reviewed in Huberman et al., 2008). Further support for this model comes from studies that show that segregation combines synaptic strengthening via LTP-like mechanisms and synaptic weakening via LTD-like mechanisms (Butts et al., 2007; Shah and Crair, 2008; Ziburkus et al., 2009). In addition, there is strong evidence that homeostatic mechanisms of plasticity exist during development to dynamically adjust and stabilize nascent synapses (Gonzalez-Islas and Wenner, 2006; Krahe and Guido, 2011; reviewed in Turrigiano and Nelson, 2004; Wenner, 2011). One interesting hypothesis is that some of the perturbations to retinal waves alter levels of activity in such a way to produce compensatory changes in synaptic strength, which may contribute to retinotopic or segregation defects.

Recently, single RGC axon reconstructions in the dLGN have revealed that eye-specific segregation involves the combination of two processes: the elaboration and refinement of appropriately targeted axon arbors together with the elimination of inappropriately targeted ones (Dhande et al., 2011) (Figure 4A). Interestingly, these two processes appear to be distinct from one another. This was recently shown using a genetic approach to selectively reduce synaptic glutamate release from ipsilateral-projecting RGCs, while otherwise maintaining normal spontaneous retinal activity (Koch et al., 2011) (refer to Figure 4B). This manipulation prevented coincident firing between ipsilateral RGC axons and their targets. Thus, a classic Hebbian model of competition would predict that these release-deficient axons should lose axonal territory to their more active counterparts. In agreement with this model, contralateral projections failed to be eliminated from the ipsilateral region. However, the ipsilateral axons refined and maintained their normal axon termination zones within the ipsilateral region. These findings therefore suggest that non-Hebbian mechanisms, requiring activation of just the presynaptic cell but not coincident activation of both pre- and postsynaptic cells, contribute to the synaptic stabilization of ipsilateral RGC axons in the dLGN. Although little is known about the mechanisms of non-Hebbian plasticity, calcium influx via voltage-dependent calcium channels or synaptic release of a factor such as a monoamine neurotransmitter could provide the molecular basis of this synaptic stabilization (Koch et al., 2011).

A similar finding was observed in another study, in which a subset of axons that normally project to the ipsilateral dLGN was genetically directed to project contralaterally (Rebsam et al., 2009) (refer to Figure 4C). This was achieved using a knockout mouse that lacks EphB1 (EphB1 KO), a molecular determinant for laterality, which is expressed in approximately 50% of ipsilateral-projecting RGCs. Eye-specific segregation was disrupted in the dLGN of EphB1 KO mice, showing significant overlap between ipsilateral and contralateral fibers compared to wild-type, perhaps as a consequence of reduced ipsilateral fiber number or altered synaptogenesis (Rebsam et al., 2009). However, the remaining ipsilateral axons refined to form a small ipsilateral region. In addition, the misrouted axons, which targeted the correct topographic location but in the opposite dLGN, segregated from the other contralateral axons and refined to form an "ectopic patch." Both the ipsilateral and ectopic patches were eliminated upon pharmacological blockade of retinal waves, indicating that their refinement was activity dependent. This finding is in contrast with a study lacking Ten-m2 (Ten-m2 KO), a member of the teneurin family of glycoproteins, which show a decreased number of ipsilateral projections but normal segregation of ipsi- and contralateral inputs

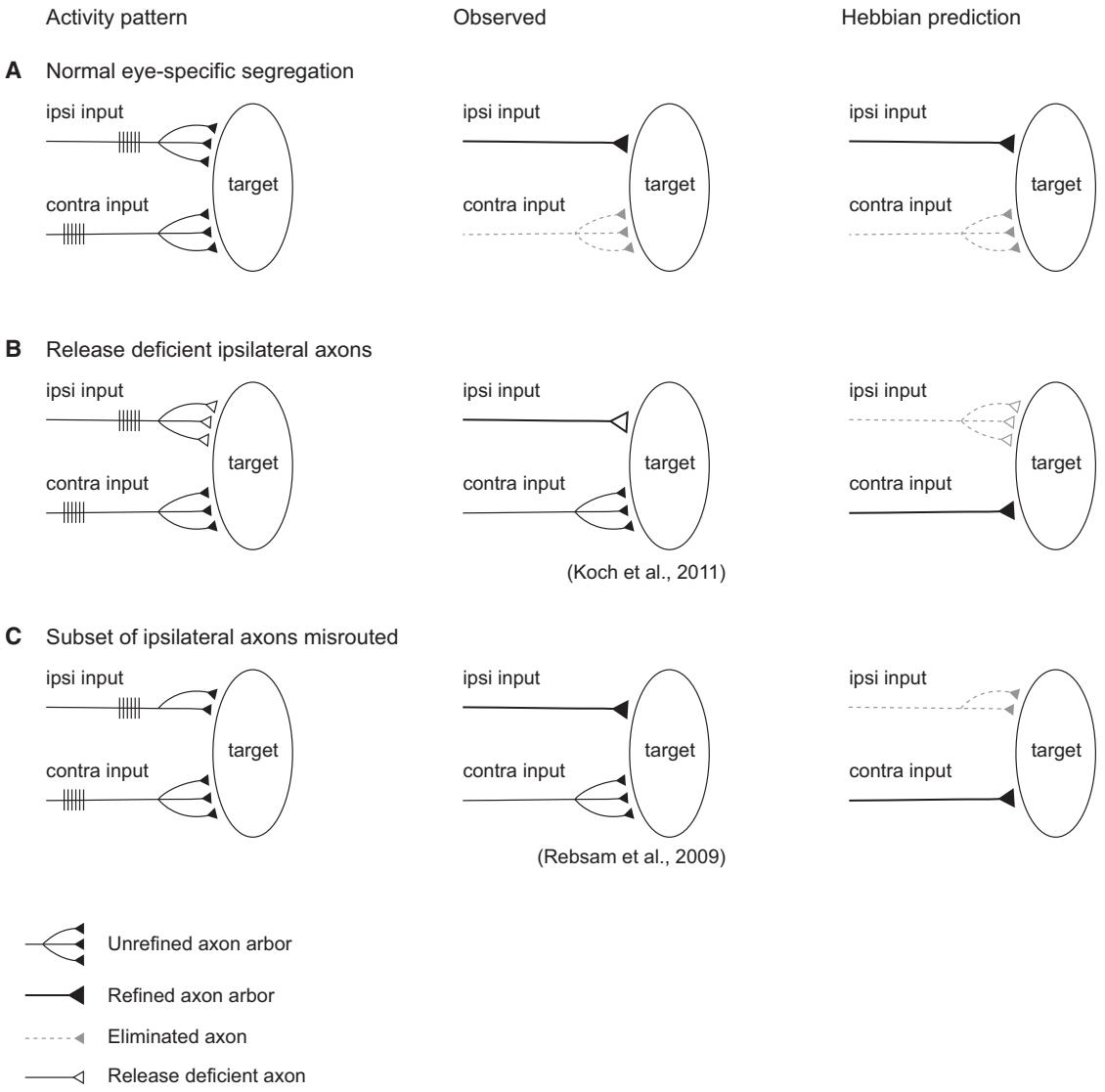


Figure 4. Activity-Dependent Competition during Eye-Specific Segregation in the dLGN under Normal and Disrupted Glutamate Release and Targeting

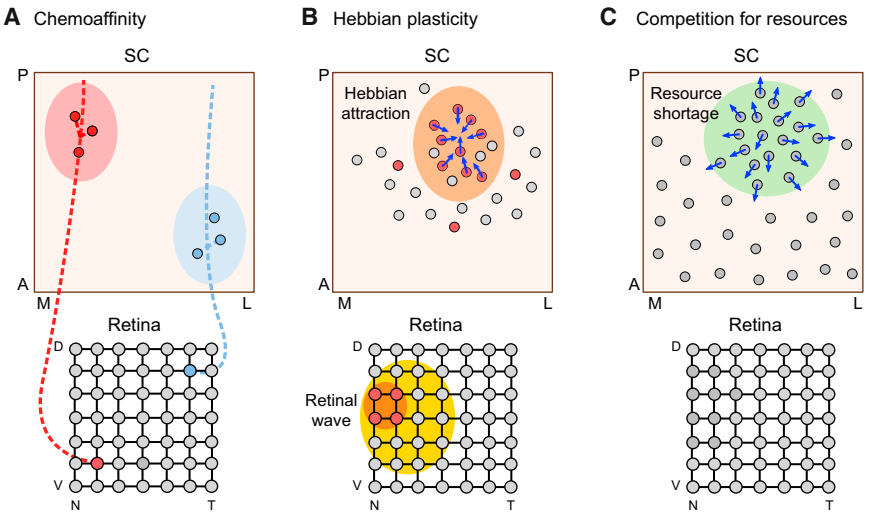
Schematic representations of activity-dependent competition during eye-specific segregation in the dLGN for normal development (A), glutamate release-deficient ipsilateral projecting axons (B), and for a subset of ipsilateral axons that was genetically misrouted to project contralaterally (C), as described in the text. Left panels show afferent activity patterns; middle panels show experimental observation; right panels show prediction according to a Hebbian model of competition.

(Young et al., 2013). It would be interesting to combine these genetic manipulations with reconstructions of single-axon termination zones to observe whether the process of axon branch refinement occurs in a similar manner to wild-type mice.

These studies are consistent with the model that the elimination of contralateral axons may follow learning rules based on Hebbian competition requiring activation of the postsynaptic cell, but that the refinement and stabilization of ipsilateral axons may depend predominantly on the activity of the presynaptic cell, thus perhaps pointing to a non-Hebbian learning rule. Recent studies have implicated activity-dependent activation of immune molecules (reviewed in Boulanger, 2009) as well as signals derived from microglia (Schafer et al., 2012) and astrocytes (reviewed in Clarke and Barres, 2013) as perhaps being key to this process.

Learning Rules for Retinotopy in the SC Differ for Monocular and Binocular Inputs

Single-axon reconstructions of RGC projections to the SC have shown that axon terminals initially ramify coarsely over their approximate termination zone, with some sparse collateral branches that overshoot the appropriate region. During development, these coarse arbors refine to precise locations, combining an increase in arbor complexity together with an elimination of inappropriate collateral branches (Dhande et al., 2011). This refinement has been shown to be dependent on the presence of distance-dependent correlated firing between neighboring



Adapted from Grimbert and Cang, 2012

Figure 5. Components Used in Theoretical Models for Retinotopic Refinement

Schematic representation of components used in theoretical models for retinotopic refinement: chemoaffinity gradients (A), Hebbian plasticity (B), and competition for resources (C). First, chemoaffinity gradients in the form of ephrin/Eph gradients guide RGC axons to their approximate retinotopic location and to form selective arborization. Second, a Hebbian plasticity component strengthens the synapses of cells that are driven to fire together by retinal waves. Third, competition for limited resources in the target areas function to constrain the termination zone of RGC axons. V, ventral; D, dorsal; T, temporal; N, nasal; A, anterior; P, posterior; M, medial; L, lateral. (Adapted with permission from Grimbert and Cang, 2012.)

RGCs, with the requirement of nearby cells being highly correlated in their firing and distant cells being uncorrelated. In this way, the target cells in the SC may act as coincident detectors that measure the proximity of the afferent RGCs to one another (reviewed in Eglen et al., 2003).

More recently, there is evidence that competition among same-eye inputs might drive retinotopic refinement in the SC (Furman and Crair, 2012; Furman et al., 2013). Whether this competition follows traditional Hebbian learning rules remains unknown. Interestingly, the presence of binocular competition perturbs normal retinotopic development. For example in β2(TG) mice, in which expression of β2-containing nAChRs is restricted to the ganglion cell layer resulting in short-range waves, the retinotopic defects seen in β2-nAChR KO mice were rescued only in monocular regions of the SC but not in the binocular (anteromedial) region (Xu et al., 2011) (Figure 2D). Similarly, when ChR2 was expressed in RGCs and stimulated to drive RGC activity, retinotopy of ipsilateral axons in the SC was perturbed when eye-specific segregation was also disrupted (during synchronous stimulation of both eyes; Figures 2G and 2H) but was normal when segregation occurred normally (during asynchronous stimulation of both eyes; Figures 2E and 2F) (Zhang et al., 2012). These observations suggest that eye-specific segregation in the SC might first be necessary in order for axons to refine into retinotopic maps, and that competition between inputs from different eyes might provide conflicting signals that obstruct retinotopic map formation. Thus, the learning rules that drive retinotopic refinement in monocular regions of the SC may be inadequate to drive refinement in the presence of binocular competition. This is in contrast to what is observed in the dLGN, where segregation and refinement appear to be somewhat independent processes.

Insights into Mechanisms of Circuit Refinement from Theoretical Models

Computational models of retinal waves have provided a means to probe how spontaneous activity patterns are generated and how they contribute to network refinement. Because many circuit elements underlying the generation and propagation of cholinergic retinal waves are known—(Ford and Feller, 2012)—modeling parameters of cholinergic waves have been based on experimental observations. This has led to the generation of models in which simulated waves closely match the spatial and temporal properties of experimentally observed waves (Ford et al., 2012; Gjorgjieva and Eglen, 2011; Godfrey and Swindale, 2007; Hennig et al., 2009; Markowitz et al., 2012).

Simulated waves generated from these models have served as input for computational studies of network refinement (Butts et al., 2007; Godfrey et al., 2009; Grimbert and Cang, 2012; Tsigankov and Koulakov, 2006; Yates et al., 2004). In general, these refinement models are made of up two parts. The first part includes molecular guidance cues and chemoaffinity ephrin/Eph gradients, which dominate the early stage of development by guiding axon growth to the correct axis, thus setting up global retinotopic structure, in agreement with experimental observation (Feldheim and O'Leary, 2010; Simpson and Goodhill, 2011; Triplett and Feldheim, 2012). The second part is based on activity-dependent processes that underlie subsequent refinement of connections and has mainly been implemented as a form of Hebbian-based plasticity, which drives refinement via burst-timing-dependent synaptic strengthening and weakening between simulated RGC axons and recipient dendritic arbors that are coincidently active (Butts et al., 2007; Godfrey et al., 2009; Grimbert and Cang, 2012; Tsigankov and Koulakov, 2006). One of the major findings produced by this approach is that burst-based learning rules that integrate activity over the 1 s timescale more accurately represent experimental data in comparison to spike-based learning rules that integrate activity over the 10 ms timescale (Butts and Kanold, 2010; Butts et al., 2007; Godfrey et al., 2009). This finding was recently confirmed with experimental data described above (Zhang et al., 2012).

Recent insights have come from models that included an additional activity-dependent component that represents axonal competition on much longer timescales than synaptic plasticity (Figure 5). For example, one model implemented a rule in which

activity-dependent axonal release of trophic factors promotes self-growth while inhibiting growth of neighboring axons (Godfrey et al., 2009). In a second example, the model implemented a rule in which activity-dependent competition for limited, preexisting resources in the target areas functioned to constrain the terminal field of RGC axons (Grimbert and Cang, 2012; Tsigankov and Koulakov, 2006). Hence, the action potentials generated from spontaneous network activity may be driving multiple activity-dependent processes functioning on different timescales. Furthermore, because these mechanisms depend on presynaptic activity but not postsynaptic activity, they might be considered a form of non-Hebbian, activity-dependent refinement.

By allowing for systematic variation of the timescales over which learning rules operate and of the spatial structure of correlated firing, models have led to a deeper understanding of what features of retinal waves might be important for driving refinement. One interesting example compares the modeling and experimental results for the effects of β2-nAChR KO firing patterns on retinotopic refinement in the SC. Though β2-nAChR KO exhibit waves, their correlation structure is distinct from WT. Specifically, WT waves show correlation patterns in which the firing properties of neighboring cells are highly correlated, whereas those of more distant cells are uncorrelated (Wong et al., 1993). β2-nAChR KO waves also show a decreasing correlation index as a function of increasing intercellular distance, but neighboring cells are less correlated than for WT waves, whereas distant cells are more correlated (Stafford et al., 2009; Sun et al., 2008a). Nonetheless, retinotopic refinement is strongly disrupted in β2-nAChR KO mice despite the underlying wave feature of a decreasing correlation index.

A potential explanation for this was provided in a recent model by Godfrey et al. (2009). In this study, refinement was found to be robust to extreme manipulations of some spatiotemporal properties of waves, such as wave velocity, frequency, and size, suggesting a limited contribution of these parameters to network refinement. This aspect of the model was experimentally confirmed by the finding that wave size did not influence retinotopy for SC regions that receive monocular input (Xu et al., 2011). When the correlation patterns of simulated waves were modified to match those observed in β2-nAChR KO mice, retinotopic refinement was impaired—axon terminals and RGC receptive field radii were 2- to 2.5-fold greater than those for simulated WT waves. However, this impairment was less severe than that observed experimentally in β2-nAChR KO mice. Hence, they concluded that the correlation properties of waves only partially contribute to retinotopy. These observations support the idea that the relative level of activity between competing cells is more significant than a cell's absolute level of activity in driving refinement and suggest that many mechanisms likely work in tandem to optimize refinement.

In summary, models of cholinergic waves and network refinement have provided a means for exploring how molecular and activity-dependent mechanisms interact. In addition, they allow researchers to make predictions and apply constraints on the underlying biological variables, as well as provide a consistency check with experiment. The accumulation of more quantitative experimental data and their application to models will offer the potential to tease apart the key processes and interactions that underlie network refinement during development.

Conclusions

Approximately two decades after the discovery of correlated spontaneous activity in developing neural circuits, there is considerable evidence that the endogenous patterns of activity drive the refinement and formation of specific features of adult circuits and sensory maps. Many insights have been gained into the learning rules that underlie how afferent patterns of activity dictate refinement of downstream targets. These learning rules likely include a combination of Hebbian and non-Hebbian activity-dependent processes, the molecular underpinnings of which remain to be elucidated. In addition, the learning rules that underlie the segregation of competing axons and the stabilization and refinement of single-axon arbors do not appear to be universal across brain regions or across cell types, illustrating that multiple factors work in tandem to achieve normal circuit formation. With the continued development of sophisticated genetic manipulations and optogenetic approaches to alter activity in constrained spatial and temporal patterns, combined with a deeper understanding of the plasticity mechanisms that decode the patterns, researchers will continue to unravel the mechanisms underlying how correlated spontaneous activity drives the maturation of nascent circuits.

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