Review

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Learning to see: patterned visual activity and the development of visual function

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To successfully interact with their environments, developing organisms need to correctly process sensory information and generate motor outputs appropriate to their size and structure. Patterned sensory experience has long been known to induce various forms of developmental plasticity that ultimately shape mature neural circuits. These same types of plasticity also allow developing organisms to respond appropriately to the external world by dynamically adapting neural circuit function to ongoing changes in brain circuitry and sensory input. Recent work on the visual systems of frogs and fish has provided an unprecedented view into how visual experience dynamically affects circuit function at many levels, ranging from gene expression to network function, ultimately leading to system-wide functional adaptations.

Patterned visual activity and the developing visual system: an overview

The survival of an organism depends on its ability to successfully interact with the environment, and for a young animal this typically begins before its nervous system has completed development. The immature nervous system, though considerably different from the adult brain, is obviously capable of providing essential functions for the animal to thrive [1]. However, as development proceeds and the organism grows, the nervous system undergoes profound activity-dependent and -independent changes both in the architecture of its neural circuitry and in the electrical properties of individual neurons within those circuits. This type of developmental plasticity has traditionally been invoked to explain how the adult brain comes to be sculpted from the immature circuit during development. In the short-term, however, plasticity also mediates important adaptive changes that help developing organisms to respond appropriately to the environment in the face of their own ongoing changes.

The visual system of vertebrates provides one of the best-studied examples of the role of sensory experience in circuit development [2]. Starting with seminal discoveries by Hubel and Wiesel [3], a long history of increasingly sophisticated experiments has implicated spatiotemporal patterns of neural activity, arising either spontaneously or through visual stimulation, in the refinement of several fundamental aspects of mammalian visual system organization; these include proper retinotopy, segregation of monocular inputs and stimulus selectivity [4–9]. Visual activity and patterned spontaneous activity are believed to guide this process through the induction of various forms of use-dependent plasticity – such as long-term potentiation (LTP) and depression (LTD) and synaptic scaling – that, over development, gradually shape the functional organization of the visual system [10–12]. However, it is also becoming evident that the visual system can adapt rapidly to changes in the visual environment to maintain stable function [13–15]. Some of the same plasticity mechanisms implicated in development are also important for these functional adaptations, although some novel ones might also be involved.

Here we review several recent studies describing the role of patterned retinal activity on the functional properties of the visual systems of developing frogs and fish, mostly in *Xenopus* tadpoles and zebrafish embryos. These studies have helped to elucidate general principles that probably extend to a variety of sensory systems across vertebrate species. External fertilization and development make fish and frogs particularly amenable to early surgical and genetic manipulations, including transplantation, dye-labeling and transfection of single cells. This has led to their increasing popularity for *in vivo* imaging and electrophysiological studies during embryonic development. The main visual center in these animals is the optic tectum that receives direct input from the retina. The output of the tectum is directly related with the activation

Glossary

Receptive field (RF): in the case of the visual system, the receptive field of a neuron is the area of visual space in which a visual stimulus will activate the neuron.
Retinotopic map: an orderly projection between the retina and a central visual area (in this case the optic tectum) in which near-neighbor relationships are maintained such that nearby cells in the retina project to nearby cells in the tectum. This maintains the relative topographical organization of visual space in the different visual areas.
Spike timing-dependent plasticity: a type of long-term synaptic plasticity in which the polarity of the change in synapse strength (either potentiation or depression) depends on the relative timing between the synaptic input and the spiking of the postsynaptic cell.
Synaptic scaling: a type of adaptive synaptic plasticity in which the synaptic strengths of all synapses in a neuron are up- or down-regulated in response to long-term decreases or increases in global levels of neural activity.

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0166-2236/$ – see front matter doi:10.1016/j.tins.2010.01.003 Available online xxxxxx

Box 1. Patterned retinal activity and the wiring of the developing visual system in frogs and fish

Visual experience participates in the structural refinement of the retinotectal projection through activity-dependent mechanisms. Is activity permissive or instructive for map plasticity? An anatomical screen for retinotectal projection defects in zebrafish [91,92] has revealed several lines in which defects in neural activity or synaptic transmission are associated with abnormal development of the retinotectal projection [24,93]. However these experiments did not distinguish between permissive and instructive roles of patterned activity.

A key aspect of instructive plasticity is that spatiotemporally patterned activity in the inputs provides the information necessary to direct the stabilization or elimination of specific connections. This might be achieved by Hebbian mechanisms in which cells with similar firing patterns should consolidate their connections whereas cells with mismatched firing patterns disconnect from one another. In mammals much of this patterned activity is generated spontaneously in the form of retinal waves before eye opening takes place. In frogs and fish the retina is already able to transmit visual information by the time RGC axons first innervate the tectum [94], permitting experiments that examine an instructive role of activity. When inputs across the entire retina are artificially correlated during development by strobe-rearing goldfish, largely eliminating instructive cues from retinal firing patterns, RGC axon arbors and receptive fields fail to refine normally [95]. Further evidence for an instructive role of neural activity comes from experiments demonstrating that pharmacological blockade of NMDA-type glutamate receptors in developing zebrafish drives an expansion of the RGC terminal arbor coverage area, suggesting that correlation detection through NMDA receptors rather than the overall activity level could be required for axonal refinement [96]. Experiments in frogs have also shown that the retinotopic precision of axonal terminations is degraded if NMDA receptors are blocked in the mature tectum [97], consistent with the idea that the same mechanisms mediating map refinement probably continue to maintain the map long after it is initially established.

The formation of eye-specific bands in the tecta of fish and frogs experimentally manipulated to have binocular innervation of the same tectal lobe constitutes the strongest evidence for an instructive role of neural activity in circuit development. In these experiments inputs from the two eyes segregate into a unique alternating ocular dominance pattern across the tectum that compromises between the constraints imposed by topographic molecular cues and activity-dependent mechanisms [98–100]. This segregation, that is dependent on neural activity in RGCs [101,102] and activation of tectal NMDA receptors [103], involves a process of stochastic extension of new branches along axons and their selective elimination from territories dominated by inputs from the other eye [104]. Taken together these studies are consistent with a model where correlated activity activates postsynaptic NMDA receptors, resulting in stabilization of the co-active inputs via Hebbian modifications, whereas inputs that are not co-active are selectively eliminated.

On the other hand, more recent studies also support the existence of non-Hebbian forms of competition. Selectively silencing individual RGCs (by transfecting them early in development with an inwardly-rectifying leak K^+ channel subunit) results in relatively smaller and less branched terminal arbors of those neurons [105]. This effect is blocked if the entire eye is silenced with tetrodotoxin, showing that competition among axons is necessary to cause retraction of the less active input. In a converse experiment, single RGCs were implanted in a zebrafish *lakritz* mutant lacking endogenous RGCs. In this experiment the axon from the single RGC grew into an appropriate tectal location, but its terminal arbor was expanded because it had no neighboring axons to compete with [106]. These experiments reveal the participation of diverse forms of competition in the refinement of the retinotectal projection.

of visually-guided behaviors [16–18], and thus it is an ideal preparation in which to study the functional development of neural circuits. Much is known about the development of the retinotectal projection that is organized topographically such that neighboring cells in the retina project to neighboring sites in the tectum [19]. Initial development of topography in this projection depends on an array of molecular cues, but its precise refinement is believed to require neural activity [20,21] (Box 1).

Whereas there is ample evidence that patterned visual activity is important for establishing the fine structure of the central visual pathways, an increasing body of evidence suggests that patterned activity is also important for fine-tuning the functional properties of the developing visual system. During the developmental time period in which the retinotectal map is being established and refined, both *Xenopus* tadpoles and zebrafish embryos are able to see and behave appropriately in response to visual stimuli [22–24]. Thus the visual system must be able to continuously adapt its response properties to respond appropriately to the visual environment, even while the neural circuitry responsible for visual processing is changing rapidly. Patterned visual activity plays an important role in instructing these adaptive changes that occur at many levels – ranging from synaptogenesis and process outgrowth to the regulation of gene expression, homeostatic adaptations of dynamic range, receptive field properties and temporal response characteristics of the tectal network (Figure 1). Each of these levels will be reviewed in turn.

Patterned activity leads to dynamic synaptogenesis and process outgrowth

A remarkable amount of neural circuit remodeling occurs late in development. For example, synapse density in the mammalian visual cortex is known to peak shortly after birth, but is subsequently reduced by intensive synaptic pruning [25,26]. The ability to even crudely process sensory information with circuits that are still in the process of undergoing developmental change is a common challenge across species. Fish and amphibians, for example, undergo extensive neurogenesis until well into maturity, and this leads ongoing expansion and distortion of topographically organized neural maps. The retina, which adds new neurons at the margin nearest the lens and expands radially, whereas the target of retinal ganglion cell (RGC) axons, the optic tectum, expands by adding new cells linearly along its periventricular proliferative zone. One consequence of this ongoing neurogenesis is the need for all RGC axonal inputs to the tectum to shift their termination zones gradually over time as the structures expand in order to maintain a relatively evenly-spaced retinotopic map [27,28]. To maintain optimal function, synaptic contacts between the eye and the brain are obliged to dissolve and reform at new sites throughout much of the life of the animal.

Early *in vivo* imaging studies in both zebrafish and *Xenopus* systems have revealed that the RGC axon terminal and the tectal dendritic arbor are remarkably dynamic structures, even in animals that actively rely on visual function to guide their behaviors [29,30]. Subsequent

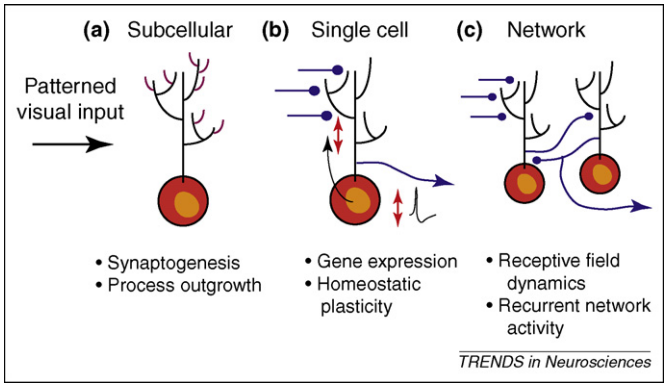

Figure 1. Rapid functional modulation of the retinotectal circuit by visual experience. Although neural activity is known to be crucial for the gradual sculpting of neural circuits over development, there is ample evidence that patterned activity also induces rapid functional adaptations that could allow for the optimization of neural circuit function in response to a changing environment and neuronal architecture. In this article we review recent studies from the visual system of frogs and fish that show that these adaptations can occur at many levels of function in the optic tectum, the principal visual area in the brains of these species. **(a)** On the subcellular scale visual activity can induce rapid changes in optic tectal neurons that involve synaptogenesis and process outgrowth. This provides a substrate for rapid experience-dependent plasticity. **(b)** At the single-cell level visual experience triggers gene expression that can have cell-wide effects, particularly in altering dendritic structure. It can also allow homeostatic adaptations in synaptic transmission and intrinsic excitability that can normalize the input–output properties of tectal neurons. **(c)** At the level of neural circuits, visual experience can modify receptive field properties of tectal neurons as well as the temporal activation pattern of recurrent circuits within the tectum.

experiments revealed that the motility of axons and dendrites is indeed not independent of visual function, but is instead directly modulated by visually driven synaptic activity [31–33]. Live-imaging experiments employing targeted expression of synaptic components tagged with green fluorescent protein (GFP), including GFP–synaptobrevin and synaptophysin–GFP fusions that reveal clusters of presynaptic vesicles in axons [34–36], and PSD95–GFP fusions that permit visualization of the postsynaptic density in dendrites [37,38], have lent support for the idea that synapses are being rapidly assembled and disassembled within the functioning but immature retinotectal projection.

An influential way of thinking about the developmental interplay between synaptogenesis and projection stability is the 'synaptotropic model' first put forward by Vaughn [37,39]. This model proposes that stabilizing interactions at synaptic contacts modulates the intrinsic tendency of cells to branch and form new synapses in such a way as to bias connectivity. Indeed considerable evidence in the retinotectal system supports the notion that synapse maturation, as measured by increased accumulation of presynaptic vesicles at presynaptic sites [35,40], or by the addition of AMPA-type glutamate receptors (AMPAR) to postsynaptic synapses [41], not only can confer additional stability onto axonal and dendritic arbors at these sites, but can also enhance local branching of these processes [34,36,37], thereby resulting in activity-regulated, local control of arbor elaboration through synaptic modulation.

Control of gene expression by visual experience

Plasticity induced by visual experience and synaptic activation does not only impact activated synapses. Neural activity is one of the major regulators of transcription in neurons, largely through the activation of voltage-gated calcium channels and calcium-dependent transcription factors. Several such transcriptional regulators have been shown to directly modulate synaptic or structural properties of developing neurons [42–45].

A calcineurin-activated transcriptional regulator – the nuclear factor in activated T-cells (NFAT) – has been implicated in the regulation of both activity-dependent structural remodeling of dendrites and in the regulation of synaptic maturation in the developing *Xenopus* visual system [46]. Low-frequency patterned visual stimulation drives the translocation of NFAT from dendrites into the nucleus of tectal neurons where it engages a transcriptional program that limits synaptic maturation and reduces neural activity-dependent dendritic branch extension (Figure 2). Importantly, inhibition of NFAT in tectal neurons not only enhances the cell-wide rates of synapse maturation and branch formation, but inhibition also modulates how the cell responds to activity changes at synaptic inputs, effectively reprogramming the cell with a new set of plasticity rules based on transcription driven by the cell's prior neural activity. Thus, neurons can respond differently to the same activity patterns depending on their recent transcriptional history.

Numerous screens for activity-regulated genes have resulted in long lists of candidate plasticity genes that increase expression within minutes of neuronal activation. Many of these turn out to play crucial roles in development and plasticity. The ease of live imaging and patch-clamp physiology in the *Xenopus* retinotectal system has permitted several striking *in vivo* demonstrations of how activity-regulated genes impact upon neural circuit development and function. For example, CPG15, also known as neuritin, was originally identified by a subtractive screen for cDNAs differentially expressed by neuronal activation of rat dentate gyrus [47]. Overexpression of CPG15 in the tadpole optic tectum caused a dramatic increase in the elaboration of tectal neuron dendrites and presynaptic axonal arbors [48,49]. These changes were accompanied by enhanced synaptic maturation revealed by the recruitment of AMPA receptors to retinotectal synapses. Another plasticity-associated gene rapidly up-regulated by visual stimulation in the developing optic tectum is the short form of Homer (Homer 1a) (Ref. [50]). In contrast to the increase in synaptic efficacy at AMPARs driven by CPG15, the visual stimulation-induced increase in Homer 1a expression was found to prevent the increase in AMPAR-mediated transmission in tectal neurons that normally occurs when mGluR1 receptors are activated.

Brain-derived neurotrophic factor (BDNF) is implicated in activity-dependent developmental plasticity and is robustly regulated at the level of transcription [51–53], translation [54], and release [55]. A series of experiments by Cohen-Cory and colleagues using *in vivo* time-lapse imaging in developing *Xenopus* tadpoles has demonstrated that BDNF in the optic tectum, that signals through TrkB receptors on RGC axons, positively regulates the axon-terminal density of GFP–synaptobrevin clusters, a marker of synapses employed in live-imaging studies [34,56]. At the same time, BDNF rapidly stabilizes RGC axon

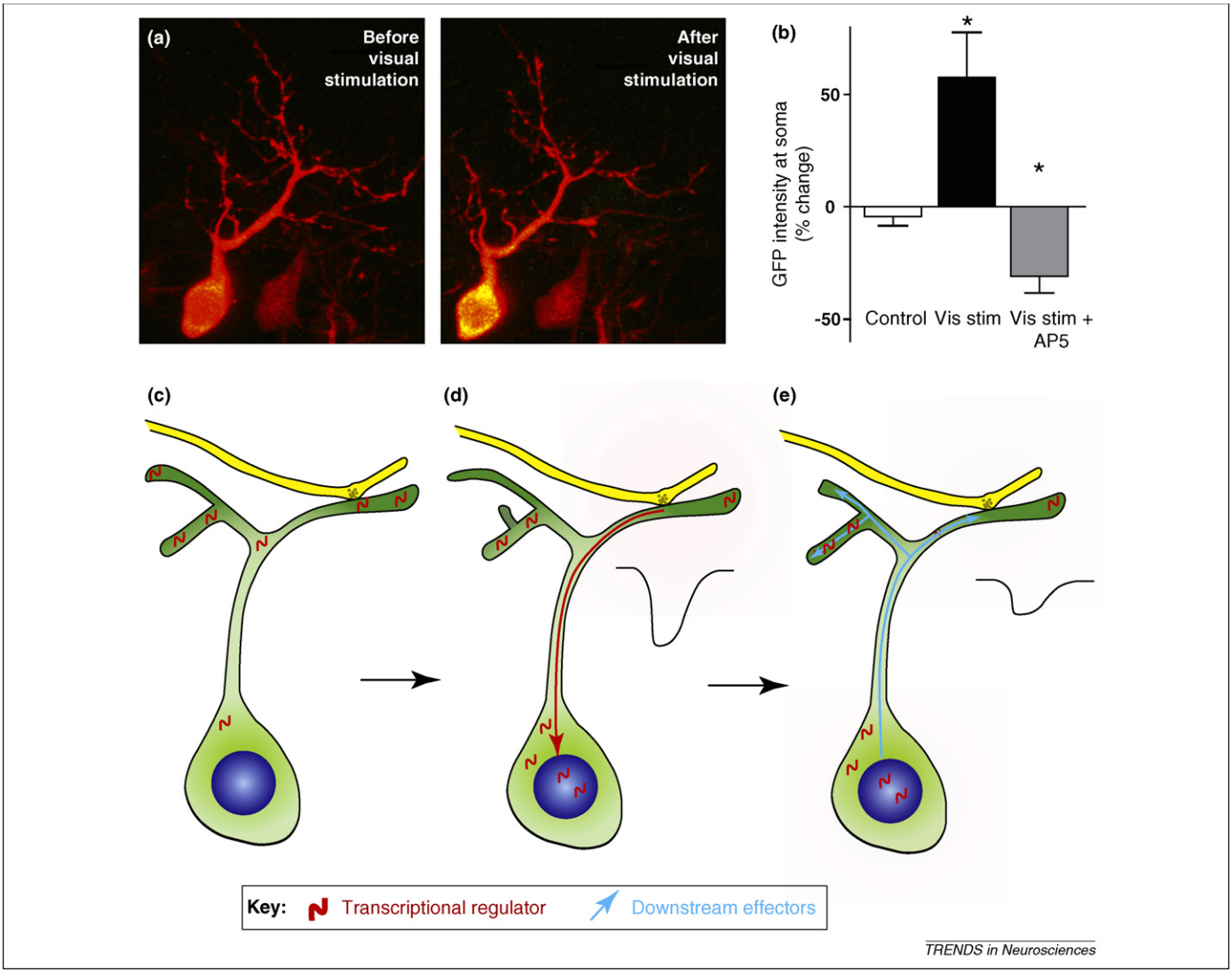

Figure 2. Activity-dependent regulation of gene transcription by NFAT (nuclear factor in activated T-cells) alters dendritic and synaptic development. In *Xenopus* tadpoles, visual stimulation causes the transcriptional regulator NFAT to translocate toward the nucleus where it drives changes in the expression levels of a number of plasticity-associated gene products. **(a)** Expression of NFAT tagged with enhanced GFP (green) in tectal neurons, co-expressing cell-filling red fluorescent tdTomato to visualize dendritic morphology, reveals an increase in NFAT–GFP fluorescence in the cell soma and nucleus with a concommitant decrease in dendritic intensity following 40 min of continuous visual stimulation. **(b)** The nuclear translocation of NFAT–GFP in response to visual stimulation requires synaptic activation of NMDA receptors. Blocking NMDA receptors prevents this translocation, even causing a decrease in nuclear NFAT–GFP levels, suggesting that basal synaptic transmission might be sufficient to drive an intermediate level of NFAT activation. **(c–e)** These data suggest that dendritic stores of NFAT, perhaps associated with synapses, translocate to the nucleus in response to NMDA receptor activation. At the nucleus NFAT regulates expression levels of gene products that control both dendritic branching and synaptogenesis or synapse maturation. Blocking NFAT activation increases both branching and mEPSC frequency. Data adapted from Schwartz *et al.* [46].

branches, thereby resulting in more complex arbors with more potential synaptic contacts [57,58]. Effects on the density of postsynaptic sites were also observed by imaging PSD95–GFP, however these appeared to be subsequent to the presynaptic changes [38]. Consistent with these results, application of exogenous BDNF to the optic tectum results in a rapid, presynaptically-mediated increase in the excitatory post-synaptic currents (EPSC) evoked in tectal neurons by RGC stimulation [59]. Dendritic trafficking of BDNF mRNA for local protein synthesis is thought to be important for BDNF-dependent synaptic plasticity in the hippocampus [54] although this has not yet been demonstrated in the retinotectal system. However, proper function of the RNA-binding protein CPEB in tectal neurons has been shown to be crucial for the development of efficient synaptic transmission in *Xenopus* [60]. Thus, CPG15, Homer and BDNF exemplify gene products whose expression is regulated by and in turn regulates the response of the circuit to sensory stimuli. It is likely that this feedback property of activity-regulated genes constitutes a fundamental mechanism for homeostatic control of neuronal excitability.

Homeostatic changes in functional response properties

In order for neurons to maximize the dynamic range of their firing rates they must be able to adapt their spike output to account for changing levels of synaptic input [61,62]. Neurons can achieve this homeostatic adaptation by at least two different strategies. In the first, neurons can adjust the strength of all of their synaptic inputs equally, thereby normalizing the overall level of synaptic activity while maintaining the relative differences between

different synaptic weights. This process is known as synaptic scaling [63]. In the second strategy, neurons can adjust their own intrinsic excitability to regulate the amount of spike output in relation to the total level of synaptic input they receive [64]. Much of the initial data describing these phenomena was derived from *in vitro* experiments in which the overall levels of neuronal activity were manipulated either pharmacologically or genetically, and where the resulting changes in synaptic strength and intrinsic excitability were measured after several days [63,65,66]. However, these phenomena have more recently also been measured *in vivo* in a variety of systems and different time-scales [15,67–70].

Both processes have been described in *Xenopus* tadpoles and are known to be modulated by visual activity both in short and long time-scales (Figure 3). Developing tectal neurons have a large proportion of AMPA receptors lacking the GluR2 subunit; this renders them permeable to Ca^{2+} and sensitive to modulation by polyamines (PAs) [71]. PAs are positively-charged molecules that bind to Ca^{2+}-permeable AMPAR in a voltage-dependent manner, resulting in inward rectification and a reduction in synaptic currents even at the resting membrane potential of the cell [72]. The synthesis of PAs is regulated by neural activity, primarily through changes in expression of ornithine decarboxylase, the rate-limiting enzyme of the PA synthesis pathway [73]. This was demonstrated in a series of experiments in which *Xenopus* tadpoles were exposed to a four-hour period of enhanced, patterned visual stimulation. Exposure to patterned visual activity resulted in an increase in PA synthesis, and this in turn resulted in an overall reduction in AMPAR-mediated synaptic transmission [71]. Furthermore, the same manipulation also caused an increase in the intrinsic excitability of tectal neurons (expressed as an increase in voltage-gated Na^+ currents), and this increase required the PA-mediated decrease in synaptic transmission, but it was not mediated directly by PAs [74]. As a result, these homeostatic adaptations allowed tectal cells to reduce their activation by background neural activity, while at the same time increasing their responses to visually-evoked events, together resulting in an enhanced signal-to-noise ratio.

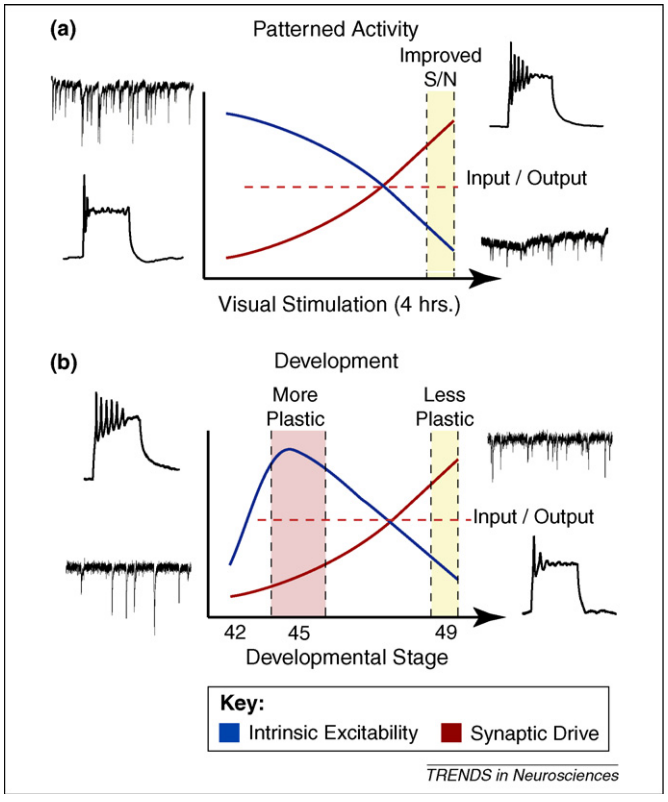

Figure 3. Homeostatic regulation of synaptic transmission and intrinsic excitability in *Xenopus* tadpole tectal neurons. Tectal cells are known to adjust their intrinsic excitability in order to maintain a broad dynamic range in response to changes in levels of synaptic input. Both short periods of patterned visual input as well as overall activity levels during development can trigger these changes, that are expressed as changes in voltage-gated Na^+ currents. In **(a)**, freely-swimming tadpoles were exposed to 4 hours of enhanced, patterned visual stimulation. This resulted in an overall decrease in spontaneous excitatory synaptic transmission caused by enhanced blockade of Ca^{2+}-permeable AMPA receptors by polyamines. As a consequence of this decrease, the amplitude of voltage-gated Na^+ currents was enhanced, increasing the intrinsic excitability of tectal cells. This combination of synaptic and intrinsic changes allows tectal cells to filter out noisy background stimuli while enhancing stimulus sensitivity to more salient visual stimuli. In **(b)**, the relationship between background spontaneous excitatory synaptic input and voltage-gated Na^+ currents was measured over development. Between developmental stages 45 and 49, tectal neurons undergo a period of rapid growth and synaptic maturation. Starting from stage 45 tectal neurons show enhanced excitability and low levels of background excitatory synaptic input. By stage 49, the amount of synaptic input dramatically increases. This results in a homeostatic downregulation of voltage-gated Na^+ currents, resulting in decreased intrinsic excitability. Both of these example illustrate how tectal neurons can dynamically adapt their intrinsic properties in response to changes in overall levels of synaptic drive. Figure based on findings from Aizenman *et al.* [71,74] and Pratt and Aizenman [68].

A similar relationship between synaptic transmission and intrinsic excitability is observed during development [68]. Between developmental stages 45 and 49, during which time the retinotectal map is being established and refined, there is an inverse relation between synaptic transmission and intrinsic excitability in tectal neurons. At the same time the net amount of excitatory synaptic drive received by tectal neurons also increases significantly. Concurrently, the intrinsic excitability of tectal cells decreases, and this decrease is mediated by changes in voltage-gated Na^+ currents. The result is that the input–output properties of the cell remain stable: when synaptic drive is weak, cells are most excitable, whereas when synaptic drive is strong, cells are less excitable. Genetic modifications decreasing excitatory synaptic transmission during development were found to prevent the observed decrease in intrinsic excitability, suggesting that the mechanisms are linked. Thus, tectal neurons are able to homeostatically maintain a wide dynamic range by altering their intrinsic excitability through the adjustment of voltage-gated Na^+ currents. This can occur gradually over development, or more rapidly in order to adapt to changing input characteristics.

Receptive field properties are dynamically regulated

Sperry's chemoaffinity hypothesis posits that guidance cues with orderly distributions in the optic tectum guide retinal axons to their proper synaptic partners along the dorsoventral and mediolateral axes [75]. Although the fundamental tenets of this model are supported by molecular-biological evidence, any complete description must also incorporate the nuances of activity-dependent developmental map refinement and receptive field (RF) plasticity [20,76]. During normal development in frogs and fish the tectum is much smaller than in the adult.

As a result, during tectal development there is a massive topographic restructuring of axons that initially overlap extensively in the smaller immature tectum [30,77]. As the tectum grows, these terminals occupy a smaller percentage of the tectum, leading to connection refinement that inevitably contributes to RF refinement. However, more recent experimental evidence reveals that activity-dependent synaptic plasticity mechanisms also have a role to play in sculpting RFs.

Taking advantage of the transparency of zebrafish larvae, Niell and co-workers carried out systematic mapping of RF properties in developing optic tecta bulk-loaded with a cell-permeant calcium indicator (Oregon Green BAPTA 1-AM) that permitted dozens of tectal neurons to be characterized simultaneously for their responses to a range of visual stimuli [78]. They observed that, from the earliest stages at which the lens forms a sharp image on the retina (70 hours post-fertilization), cells exhibit stimulus-selectivity that closely resembles that seen in mature fish – including direction-selectivity, responsiveness to moving spots and to spots flashed in the RF. However a modest increase in selectivity for all of these features was reported with age, most notably a more reliable response was evoked by small spots within the RF, indicative of improved visual acuity.

In agreement with these findings, whole-cell recordings of visually evoked synaptic potentials, made in *Xenopus* tectal neurons at different stages of development, similarly revealed an incremental improvement in the visual acuity of older animals [22,79]. Interestingly, dark-rearing had little impact on the development of these properties in zebrafish, although visual acuity was slightly reduced, suggesting that they could either develop as part of an intrinsic program or that spontaneous activity is able to instruct the development of the circuit. In support of a role for activity, disruption of normal sensory-evoked activity in *Xenopus* tadpoles by pharmacologically disrupting normal synaptic transmission through NMDA receptors or GABA receptors, was found to abrogate the improvement in visual acuity that normally takes place. Furthermore, *blumenkohl* mutant zebrafish, that have defects in neurotransmitter release, exhibit larger RGC terminal arbors, expanded RFs, and have reduced visual acuity compared to wildtype fish [24].

The strongest evidence to support a role for visual experience in the development of RF properties comes from experiments in which specific patterns of retinotectal activation or visual stimulation are applied to drive predictable changes in the RF. Retinotectal synapses in *Xenopus* tadpoles exhibit spike timing-dependent LTP and LTD [80]. By carefully timing the firing of an action potential in a tectal neuron with respect to the arrival of visually evoked EPSPs in a conditioning stimulus designed to induce either potentiation or depression, Vislay-Meltzer and colleagues were able to effectively remodel the shape of receptive fields of tectal neurons in tadpoles [81] (Figure 4). In addition to simple properties such as visual field location, conditioning stimuli have also been used to modulate more complex properties including the direction-selectivity of tectal neurons that involves both retinotectal inputs and intrinsic tectal circuitry [23]. Training by repeated presentation of directional stimuli modifies the responses of tectal neurons such that cells shift their preference to fire more vigorously when presented with bars sweeping in the trained direction [82,83].

Do these experience-dependent modifications of RF properties reflect the same mechanisms that ultimately form mature RFs, or are they a means for rapid but transient modulation of RFs? Most of the phenomena described above turn out to be disappointingly labile. They persist as long as tectal cells are maintained in a quiescent state, but once spontaneous firing resumes the cells tend to return to their previous states. Importantly, stable changes are produced when conditioning epochs are properly spaced in time rather than presented as a single massed training [84]. The implication for the functional processing of visual inputs is that the neural processing landscape is far more dynamic than is generally considered. Certain patterns of activity could indeed underlie the long-lasting modifications of tectal RFs that underlie map refinement, but there are also many and more transient modulations of neuronal response properties that reflect recent sensory experience.

Temporal network properties can be sculpted by visual inputs

Patterned visual activity not only affects retinotectal inputs but can also shape the response properties of local intratectal circuitry. Intratectal circuits represent a large proportion of synaptic inputs received by tectal neurons [85]. These local circuits are important for coordinating the activity of the tectal network output and are important for generating precise visual avoidance behavior and could also be a substrate for rapid modulation of RF properties [22]. Over development, changes are observed in the temporal dynamics of local network activity within the *Xenopus* tadpole tectum, such that recurrent network activity – initially triggered by incoming retinal input – becomes more temporally coherent and less variable, increasing the precision of tectal cell spiking [68].

How does this refinement of local circuits occur? One possibility is that temporal properties of recurrent tectal circuits are sculpted by incoming retinal input, perhaps via a timing-dependent synaptic plasticity rule. If so, then if a visual stimulus is repeated at a specific time interval, a trace of this interval should be detectable in the pattern of recurrent activity evoked by single stimuli. In a series of *in vivo* experiments Pratt *et al.* tested this hypothesis by presenting freely-swimming tadpoles with pairs of light flashes with an inter-stimulus interval (ISI) of either 150 msec or 400 msec over a period of 4 hours [85]. RGCs are known to fire bursts in response to a single visual stimulus [86], however by imposing a specific ISI during training, this interval would be overrepresented in the input frequencies received by tectal neurons. Thus, visual input in tadpoles trained with a short interval is predicted to elicit recurrent activity at a shorter latency than in those trained with the longer interval. This prediction was borne out – after 4 hours of training, tadpoles trained with the short ISI exhibited recurrent network activity in response to single optic-nerve shocks lasting a significantly shorter time than in tadpoles trained with the longer ISI. A similar

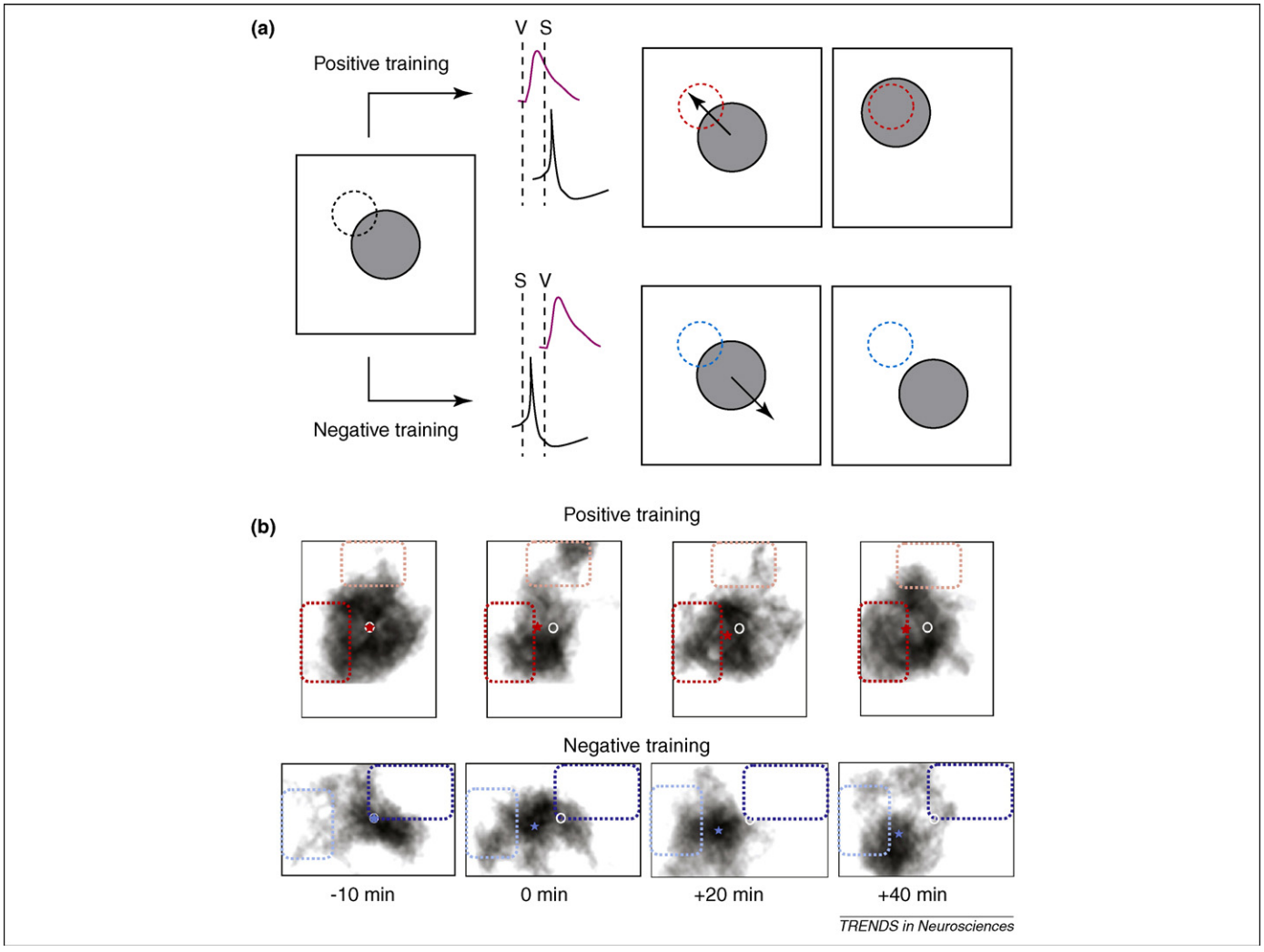

Figure 4. Patterned visual activity can dynamically alter the spatial properties of tectal neuron receptive fields. Whereas visual activity-induced synaptic plasticity has been long believed to play a role in refinement of retinotopic maps, this same type of plasticity can also rapidly alter the functional response properties of visual neurons, including retinotopy. In this example Engert and colleagues use a spike timing-dependent plasticity (STDP) protocol to alter the spatial location of tectal cell receptive fields in *Xenopus* tadpoles. **(a)** Training protocol for inducing (STDP) of receptive field location. After rapidly mapping the receptive field of a tectal neuron from which whole-cell recordings are being performed, either a positive or a negative training protocol was administered. In the positive training, an area of visual space on the edge of the receptive field was activated to induce a visual stimulus. In the diagram the receptive field is indicated by the gray circle and the training area by the dotted circle. A few milliseconds after the visual input activated the tectal cell, the cell was briefly depolarized to generate an action potential. Based on a STDP rule where the visual input (V) occurs before the spike (S), this would result in potentiation of the visual inputs on the edge of the receptive field, and would eventually cause a shift of the receptive field center *towards* the training area. In the negative training protocol, the neuron is made to spike a few milliseconds before the visual input arrives (S before V). This would result in depression of the visual input and a shift in the receptive field center away from the training area. **(b)** Representative data showing the results of positive and negative conditioning. The black blob is the map of the visual receptive field. The darker dotted areas represent the training areas. The white circle is the original receptive field center and the star represents the receptive field center during and after conditioning. Notice the shift of the receptive field center towards or away from the positively or negatively trained areas, respectively. Data adapted from Vislay-Meltzer *et al.* [81].

finding was obtained *in vitro* where the temporal pattern of recurrent activity evoked by direct optic-nerve stimulation could be conditioned to organize itself temporally around a precisely controlled time interval. This suggests that this type of network plasticity is expressed within the tectal circuitry, and can be explained by a mechanism involving spike timing-dependent plasticity of recurrent intratectal connections. These data suggest that temporal sculpting of local excitatory tectal circuits allows inappropriately timed recurrent inputs to weaken, and appropriately timed inputs to potentiate, resulting in a gradual increase in temporal coherence and in increased precision of network-driven tectal spiking. Moreover these changes can occur within a few hours, modulating the network dynamics to adapt to changing temporal input patterns.

Entraining network activity by repetition of temporally-spaced stimuli was previously described in the retinas of fish, reptiles, amphibians and mammals [87–89]. In a phenomenon known as an 'omitted stimulus potential', repetitive presentation of a given stimulus results in a response timed to match the stimulus interval in trials in which the actual stimulus was absent. A similar phenomenon was recently described by Sumbre *et al.* in larval zebrafish optic tectum [90]. In this study the authors used Ca^{2+}-sensitive dyes to image tectal cell activity in response to repetitive visual stimuli. They found that after presenting a series of evenly-spaced stimuli, a subset of tectal neurons remained entrained after the end of the stimulus train, and the timing of their post-stimulus activation matched the ISI of the stimulus. Interestingly, the authors

Box 2. Outstanding questions

A number of outstanding questions regarding short-term developmental plasticity remain unresolved, and these cover the gamut from mechanism to behavior. Here we highlight several of the key topics that should be the subject of future investigations.

Dynamic synaptogenesis and outgrowth

- Is the dynamic behavior of axons and dendrites observed during the initial formation of the map subject to regulation by the same mechanisms that maintain the map in older animals as the brain grows?
- The axonal and dendritic arbors, as well as the pre- and postsynaptic structures, have thus far only rarely been imaged together in the central nervous system. What is the prevalence of transient hemisynapses (in which only pre- or postsynaptic elements are present), and how does the association of pre- with postsynaptic structure contribute to relative stability of the arbors and synapses? What are the trans-synaptic signaling pathways that contribute to structural plasticity?
- How many cell types are there in the retinotectal circuit? Do they each respond differently to sensory stimulation? Enhancer-trap experiments will be useful for better characterizing the range of cell types.

Regulation of gene expression by experience

- The list of activity-regulated genes that participate in circuit plasticity is far from complete. Even for BDNF, for which much is known, the detailed signaling cascades by which it exerts its effects on synapse formation, plasticity, and function are still poorly understood. More work will be required to reveal of all the players involved and how they function.
- Synaptic activity appears to regulate subcellular trafficking of some mRNAs for local protein synthesis. What are consequences of local protein synthesis in circuit function and plasticity during development?
- How do microRNAs modulate the signaling underlying such events?

Homeostasis in response properties

- What are the molecular sensors and transcriptional regulators that read neuronal activity levels to drive homeostatic adaptation such as synaptic scaling and changes in intrinsic excitability?

Receptive field plasticity

- Do the spike timing-dependent mechanisms that acutely modify RF structure in immature animals also contribute to long-term refinement of RFs seen over development?
- What is the range of changes in local tectal circuitry that contributes to RF plasticity, including tectotectal excitatory and inhibitory inputs?

Temporal properties of networks

- The zebrafish visual circuit can entrain to stimuli with ISI of many seconds. Are there specific pacemaker cells or circuits that participate in this process or is this an emergent property of the network?
- How does spatial and temporal RF plasticity contribute to the complex behavior of the organism?
- What kinds of reinforcement signals from higher brain structures might guide RF spatiotemporal plasticity in a behaviorally relevant manner?

used much longer ISIs (ranging from 4 to 10 sec) than used in the *Xenopus* study described above, suggesting that a very different, and as yet still unknown, neural mechanism could be used to entrain the network activity.

Both of these studies show that temporally-organized activity originating from the retina can allow the intratectal circuitry to self-organize, possibly optimizing the temporal response properties of the tectal network. Whereas the functional consequences of this temporal adaptation remain poorly understood, it is known that properly timed tectal activity is required for generating normal visual avoidance behavior [22], and therefore this process could be important for fine-tuning of sensorimotor integration in these species.

Conclusions

Neural processing involves the precise synthesis of circuit wiring, signaling between elements and the well-timed integration performed by each element in the circuit. Given the enormous challenges in constructing a functional brain circuit, it has been tempting to consider developmental plasticity as a process that is solely dedicated to the task of building a mature brain. However, this oversimplification ignores the remarkable degree of dynamism observed at the molecular, structural, and functional levels in developing neurons and nervous systems (Box 2). The experiments described above offer the insight that the developing circuit is not merely an unrefined version of its future self, but also a sublime reflection of its past history, its prior experience. The developing organism is not merely a miniature version of the adult, but has specific sensory processing requirements appropriate to its size and structure. While the organism develops and grows its brain must continually adapt and refine itself while simultaneously functioning as required to process and respond appropriately to ongoing sensory input.

Acknowledgements

C.D.A. is supported by the National Science Foundation, National Institutes of Health, and the Whitehall Foundation; additional funding was provided by a generous gift of the Klingenstein Fund. E.S.R. holds a Canada Research Chair and is supported by grants from the Canadian Institutes for Health Research, the EJLB Foundation, and the National Alliance for Research on Schizophrenia and Depression.

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