Modeling the Emergence of Circuit Organization and Function during Development

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Developing neural circuits show unique patterns of spontaneous activity and structured network connectivity shaped by diverse activity-dependent plasticity mechanisms. Based on extensive experimental work characterizing patterns of spontaneous activity in different brain regions over development, theoretical and computational models have played an important role in delineating the generation and function of individual features of spontaneous activity and their role in the plasticity-driven formation of circuit connectivity. Here, we review recent modeling efforts that explore how the developing cortex and hippocampus generate spontaneous activity, focusing on specific connectivity profiles and the gradual strengthening of inhibition as the key drivers behind the observed developmental changes in spontaneous activity. We then discuss computational models that mechanistically explore how different plasticity mechanisms use this spontaneous activity to instruct the formation and refinement of circuit connectivity, from the formation of single neuron receptive fields to sensory feature maps and recurrent architectures. We end by highlighting several open challenges regarding the functional implications of the discussed circuit changes, wherein models could provide the missing step linking immature developmental and mature adult information processing capabilities.

Development is a complex, protracted, and dynamic process over which multiple mechanisms interact to establish the organization and function of adult neural circuits. Although early development is primarily driven by genetic programs, activity-dependent processes play a crucial role in refining network connectivity and shaping the emergence of functional properties. Before the onset of sensory experience, many developing neural circuits generate spontaneous activity with nonrandom spatiotemporal correlations that change as the animal matures. An emerging viewpoint is that this activity, via activity-dependent synaptic plasticity mechanisms, drives refinements underlying the emergence of circuit function. With the recent advent of new technologies to simultaneously record the activity of many neurons over a prolonged time period, we have begun to characterize how synaptic, cellular, and population activity features evolve over development. A key challenge in understanding circuit development lies in deciphering how such spontaneous activity is generated in early networks and how it could shape and refine network connectivity by activity-dependent synaptic plasticity. Theoretical frameworks and computational models offer a

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powerful means to investigate this process by proposing and exploring specific hypotheses and to provide unique insights into the mechanisms shaping neural circuitry and function.

Here, we highlight recent contributions of theoretical and computational studies to our understanding of activity-dependent developmental processes, focusing mainly on sensory systems and the hippocampus in rodents. We first discuss models that shed light on the generation of early spontaneous activity characterized by synchronous bursts or propagating waves at or shortly after birth, and the progressive decorrelation and sparsification of such activity over subsequent stages of development. We then consider how in silico simulated scenarios can inform how spontaneous activity patterns shape circuit refinements via activity-dependent plasticity mechanisms, leading to the emergence of input selectivity and refined processing capabilities. Beyond establishing feedforward receptive fields and tuning properties between the sensory periphery and downstream regions, we also focus on how recurrent network structures are established downstream, and the role of inhibitory synaptic plasticity in this refinement process.

SPONTANEOUS ACTIVITY IN DEVELOPING CIRCUITS

Before the onset of sensory experience, neuronal networks in the developing brain are not merely silent. Instead, they spontaneously generate patterns of electrical activity that play a crucial role in establishing and refining neural circuits. Early in development, this activity typically takes the form of synchronous bursts, oscillations, or traveling waves, which punctuate periods of baseline quiescence and transiently activate large numbers of neurons at the same time (Khazipov et al. 2004; Yang et al. 2009; Seelke and Blumberg 2010). As development progresses, neurons can sustain higher baseline firing rates but display less correlated firing (Golshani et al. 2009; Colonnese et al. 2010; Chini et al. 2022). Spontaneous network activity also becomes sparser, activating fewer neurons at any given time (Kerr et al. 2005; Rochefort et al. 2009; Frye and MacLean 2016; Wosniack et al. 2021). This transition from intermittent synchronous bursting to sustained and decorrelated spontaneous activity reflects the maturation of neural circuits toward a system capable of precise, reliable, and efficient stimulus encoding in adulthood (Gjorgjieva et al. 2014; Avitan et al. 2021; Glanz et al. 2021; Jia et al. 2022; Trägenap et al. 2023). Experiments have identified multiple factors that influence this shift, including changes in intrinsic neuronal properties, synaptic transmission, and connectivity motifs (Mease et al. 2013; Lohmann and Kessels 2014; Pouchelon et al. 2021; Kalemaki et al. 2022). Theoretical models can help to disentangle the contribution of these factors and propose mechanisms behind the generation of spontaneous activity observed experimentally. Here, we first highlight recent theoretical work that addresses the generation of early synchronous events and the developmental shift toward progressively sparser, decorrelated, and persistent activity.

GENERATION OF SYNCHRONOUS NETWORK EVENTS IN EARLY DEVELOPMENT

Transient bursts or waves of neural activity that synchronize large networks of neurons are a key signature of early brain development and have been observed across regions and developmental stages (Hanganu et al. 2006; Golshani et al. 2009; Ackman et al. 2012; Kirmse et al. 2015; Smith et al. 2018; for review, see Martini et al. 2021). Generated spontaneously before the onset of mature sensory transduction or refined motor abilities, these events lack any obvious correlate or trigger in the external world. In peripheral sensory areas such as the retina and cochlea, specific intrinsic neuronal mechanisms enable neurons to spontaneously burst (Blankenship and Feller 2010; Ackman et al. 2012; Wang and Bergles 2015). For example, before eye opening (~P15 in rodents), the retina generates bursts of action potentials that exhibit strong spatiotemporal correlations and propagate as waves, known as retinal waves. Experimental work has classified retinal waves into three different developmental stages based on their spatiotemporal properties and the mechanisms of generation (Blankenship and Feller 2010). Theoretical models have been central to understanding retinal waves, including the mechanisms for their initiation, propagation, and termination, focusing on the interaction between intrinsic neuronal properties and electrical or synaptic transmission, reviewed in Godfrey and Eglen (2009) and Gjorgjieva and Eglen (2011).

The early developmental spontaneous events in the sensory periphery propagate to the cortex, where they can trigger the synchronous activation of local networks. In rodents, in vivo electrophysiology has identified spindle bursts, transient oscillations of the local field potential (LFP) present during the first postnatal week in the somatosensory (Khazipov et al. 2004; Minlebaev et al. 2007), visual (Hanganu et al. 2006; Colonnese et al. 2010), motor (An et al. 2014), and prefrontal cortex (Fig. 1A; Brockmann et al. 2011). In human preterm babies, these events are observed at a stage

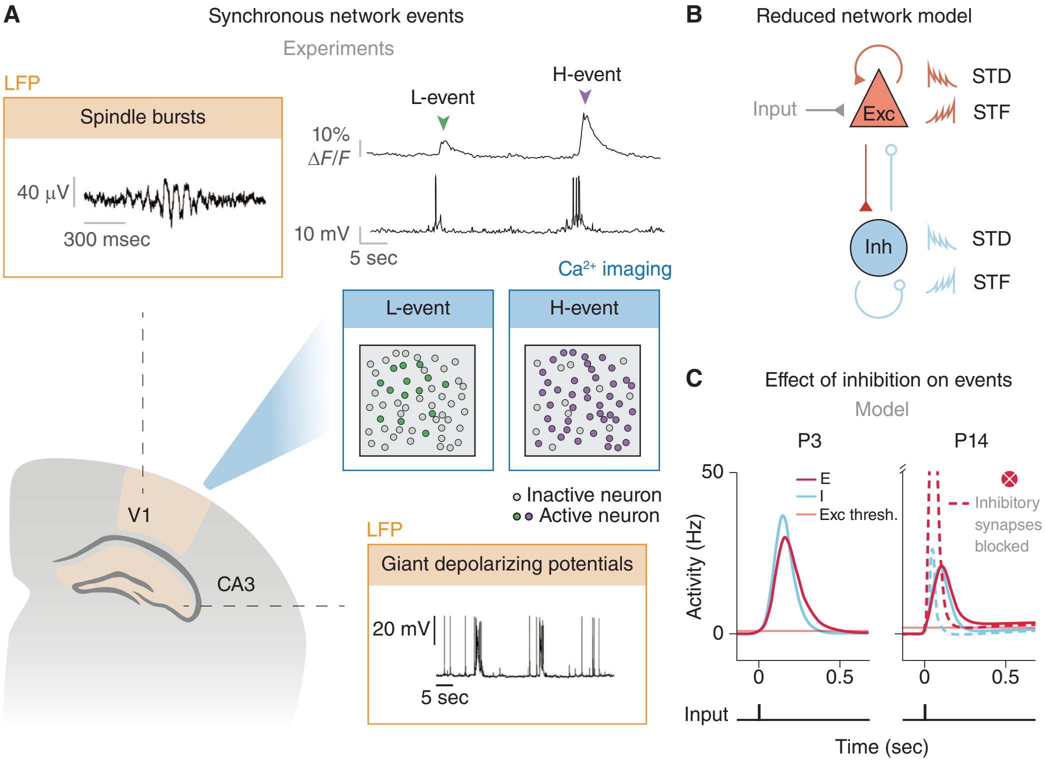

Figure 1. Spontaneous activity in the cortex: experiments and models. (*A*) Developmental spontaneous activity is most commonly observed in the cortex and hippocampus through electrophysiological local field potential (LFP) recordings or calcium imaging. Shown are representative traces of spindle bursts (LFP recordings in V1; based on data in Hanganu et al. 2006), low-synchronicity L-events, and high-synchronicity H-events (calcium imaging in V1; based on data in Siegel et al. 2012 and Leighton et al. 2021), and giant depolarizing potentials (GDPs; whole-cell patch-clamp recordings in CA3; based on data in Lombardi et al. 2018). (*B*) Reduced mean-field model of a recurrent EI network with short-term plastic connections (based on data in Rahmati et al. 2017). All excitatory (red) and inhibitory (blue) synapses are subject to short-term depression (STD) and short-term facilitation (STF). The model generates bursts of spontaneous activity reflective of spindle bursts or GDPs in response to input perturbations. (*C*) Providing a pulse input to the excitatory population leads to a large network event (*left*), which is terminated by STD in the excitatory connections. The model captures several developmental trends observed experimentally, including the reduction in amplitude of network events in the second postnatal week when inhibitory synaptic strength is stronger, and accordingly larger events when inhibition is blocked (*right*). (Simulations based on Rahmati et al. 2017.)

before eye opening in rodents and correspond to delta brush oscillations in noninvasive electroencephalogram (EEG) imaging (Milh et al. 2007). Spindle bursts in sensory cortices are elicited by activity occurring in the respective sense organs; for example, spindle bursts occurring in somatosensory and motor cortices are driven by spontaneous movements and myoclonic twitches (Kreider and Blumberg 2000; Khazipov et al. 2004; Blumberg et al. 2013), and those in the visual cortex are triggered by retinal waves (Hanganu et al. 2006). During the second postnatal week, two-photon Ca^{2+} imaging in the mouse primary visual cortex has found that the spindle bursts triggered by retinal waves manifest as low-synchronicity events known as L-events, which have low cell participation (20%–80% in a recorded population of 50–100 cells) and low amplitude (Siegel et al. 2012; Leighton et al. 2021; Tezuka et al. 2022). Such events occur alongside high-synchronicity events with a much higher cell participation (>80%) known as H-events, which have a high amplitude and are largely independent of retinal drive (Fig. 1A; Hanganu et al. 2006; Siegel et al. 2012; Leighton et al. 2021; Tezuka et al. 2022). Wide-field Ca^{2+} imaging of spontaneous activity during the same time period also identified two types of events with local and global spatial spread, and linked them, respectively, to the putative L- and H-events measured with two-photon imaging based on similar amplitudes and frequencies (Ackman et al. 2012; Gribizis et al. 2019; Leighton et al. 2021).

A class of theoretical models has provided important insight into the generation and spatiotemporal evolution of these periphery-driven spontaneous events in the sensory cortex from a dynamical systems perspective. Known as mean-field models, these network models consist of coupled excitatory and inhibitory units that represent the mean activity of a cortical network by averaging entire excitatory and inhibitory populations and individual synaptic properties (Fig. 1B). Constrained with neuronal and synaptic parameters from early development, Rahmati et al. (2017) used a mean-field model to demonstrate that events such as spindle bursts can be initiated when peripheral inputs drive the cortical excitatory population above an intrinsic threshold of instability (Fig. 1C; Rahmati et al. 2017). Specifically, when using parameters corresponding to early developmental stages (P3–P10, rodent visual cortex), the model network remains silent in the absence of input, consistent with postnatal circuits being largely quiescent at rest. In the framework of dynamical systems, this corresponds to having a single stable fixed point at a firing rate of zero, to which the network returns after a small perturbation triggered by the peripheral drive. However, introducing short-term plasticity (STP) to the synaptic weights allows supra-threshold inputs to the excitatory population to be first amplified and then attenuated, producing a transient network event that strongly activates both excitatory and inhibitory populations. This event is reminiscent of experimentally observed spindle bursts that recruit both glutamatergic pyramidal neurons and GABAergic interneurons (Khazipov et al. 2004; Hanganu et al. 2006). Mathematical analysis revealed that this network event arises from a second, transient fixed point embedded in the network's fast-firing dynamics, which is induced by the external input and vanishes because of short-term depression at excitatory synapses after the network event reaches peak amplitude.

Inhibitory activity has been difficult to characterize experimentally in early development because parvalbumin (PV), a protein expressed by the main subtype of inhibitory interneurons, is expressed late, hence prohibiting calcium imaging (see, e.g., Leighton et al. 2021; Pouchelon et al. 2021; Baruchin et al. 2022), and the onset of inhibitory influence has been the subject of frequent debate. GABAergic interneurons are slow to acquire their adult inhibitory properties, but the exact timescale over which inhibition develops in the in vivo sensory cortex and its role in regulating cortical dynamics at this stage remain unclear (Kirmse et al. 2015; Valeeva et al. 2016; Murata and Colonnese 2020; Peerboom and Wierenga 2021). In addition to being amenable to mathematical analysis, the mean-field model discussed above was also used to study the role of inhibition in generating spontaneous activity, specifically in modulating the initiation and spatiotemporal properties of network events (Rahmati et al. 2017). First, when using parameters based on the first postnatal week when inhibitory synaptic strength is weak, network events can be easily triggered. However, when using parameters based on the second postnatal week when inhibitory synaptic strength is stronger, network events become harder to generate. Simulating blocked inhibition at this later stage results in network events with much larger amplitude, implying that the developmental strengthening of inhibition suppresses network events (Fig. 1C). This supports recent experimental findings that GABAergic interneurons already exert an inhibitory effect in the cortical network by the second postnatal week (Kirmse et al. 2015; Valeeva et al. 2016; Che et al. 2018; Murata and Colonnese 2020; Leighton et al. 2021) and suppress synchronous events occurring in sensory cortices at this time (Duan et al. 2020). Indeed, recent in vivo Ca^{2+} imaging and electrophysiological recordings have identified strong inhibition from somatostatin-expressing (SST) interneurons as the main factor controlling the ratio between H-events and spindle-burst-like L-events (Leighton et al. 2021) and restricting the recruitment of excitatory neurons into L-events.

In the developing hippocampus, certain patterns of spontaneous activity are believed to rely on mechanisms endogenous to the local circuit, in contrast to the periphery-driven events in the sensory cortex. Electrophysiological recordings in slices throughout the first postnatal week have characterized one of the most prominent activity patterns in hippocampal areas CA1 and CA3, giant depolarizing potentials (GDPs). Spontaneously active excitatory pyramidal cells with strong recurrent connections are commonly assumed responsible for the initiation of GDPs (Griguoli and Cherubini 2017). As in the cortex (Rahmati et al. 2017), the same class of theoretical mean-field models has also been used to understand the generation of in vivo events likely corresponding to GDPs in the hippocampus (Graf et al. 2022). Dynamical systems analysis of the model revealed an input-dependent transition between two states in the network: first, a silent state with a fixed point at zero firing rate in which input perturbations to the excitatory population trigger GDPs via intrinsic instability-driven dynamics, and, second, an active state with an additional fixed point at a nonzero firing rate in which activity is continuous and GDPs cannot be generated. Simulating the developmental strengthening of inhibitory synapses allows the network to spend more time in the active state, which the authors relate to an experimentally observed transition from discontinuous to continuous activity in mouse hippocampus during the second postnatal week (Graf et al. 2022).

As in the sensory cortex, GABAergic interneurons have also been found to play an important role in shaping the properties of GDPs and network events at early postnatal stages in the hippocampus, both in vitro (Flossmann et al. 2019) and in vivo (Dard et al. 2022). Ca^{2+} imaging, electrophysiology, and optogenetic manipulation in vitro have revealed an excitatory role of GABA during the first postnatal week, finding that the activation of GABAergic SST interneurons can strongly promote GDPs during this time (Flossmann et al. 2019). Further analysis of the aforementioned mean-field model revealed that an excitatory action of GABA may support GDP initiation by modulating the intrinsic threshold of instability of the excitatory population (Flossmann et al. 2019). These studies exemplify the effectiveness of reduced models in identifying key features of network dynamics conducive to synchronous network events, such as instability thresholds and STP mechanisms.

The distribution of synaptic connections and single-neuron properties within a network—typically averaged out in the mean-field models discussed earlier—may also be central to generating synchronous network events. Indeed, electrophysiological and imaging experiments have identified GABAergic interneurons (putative SST neurons identified in Flossmann et al. 2019) in both CA1 and CA3 of the hippocampus to be "functional hubs," whose single-neuron stimulation can influence the activity of the entire population (Bonifazi et al. 2009; Picardo et al. 2011). These functional hub neurons have been shown in vitro to synchronize network-wide activity within CA1 and CA3 and thus orchestrate GDPs at the single-neuron level in the first postnatal week (Bonifazi et al. 2009), consistent with a potentially excitatory action of GABA at this stage. Modeling work suggests that such functional hubs may arise because of the unique combination of network topology and intrinsic cellular excitability present in the hippocampus during early development. In developing networks, both early-born, "mature" neurons and later-born, "young" neurons coexist simultaneously, because different neuronal populations mature at different rates. Assuming that younger neurons are more excitable but more sparsely connected, whereas more mature neurons are less excitable but more densely connected (Doetsch and Hen 2005; Ge et al. 2006; Picardo et al. 2011), Luccioli et al. (2014) showed in a spiking network model of excitatory neurons that this developmental heterogeneity in neuronal maturity could give rise to the existence of functional hubs. In the model, functional hubs were identified as highly excitable neurons that were the first to activate upon the onset of a synchronous network burst and could strongly impact network dynamics upon single-neuron stimulation. Because activity in the entorhinal cortex drives the maturation of the hippocampus, Donato et al. (2017) and Mòdol et al. (2017) investigated functional connectivity in the entorhinal cortex and found similar hub neurons. They further identified a second class of interneurons called low functional connected drivers, capable of impacting network dynamics when stimulated but not reliably activated at the onset of network bursts. The earlier maturation of the entorhinal cortex compared to CA3 and CA1 (Donato et al. 2017) suggests a higher probability of finding interneurons with more adult-like, inhibitory neurotransmission. Indeed, by including inhibitory neurons in the model of excitatory neurons with developmental heterogeneity, Luccioli et al. (2018) could explain the presence of low functionally connected driver cells. Together, these models highlight how the ability of single neurons to orchestrate diverse network-wide dynamics can emerge from the specific interaction between connectivity profiles, excitability, and neurotransmission present in different regions of the neonatal brain.

The same factors may also influence the spatial structure of spontaneous activity patterns across developmental ages and species. In the ferret, multiple cortices (visual, auditory, and parietal cortex) show modular patterns of spontaneous activity with long-range spatial correlations (Smith et al. 2018; Powell et al. 2022), different from the spindle bursts, L-events, or H-events in the mouse visual cortex. In the visual cortex, these modular patterns are present before eye opening and are independent of the retinal drive, suggesting their generation relies on recurrent connectivity within the cortex. However, at this age, long-range horizontal connections between orientation-selective neurons have not yet been established. Long-range activity correlations can nonetheless arise from heterogeneously oriented, elliptical connectivity profiles that induce directions of local facilitation and lateral suppression and allow activity to spread through neighboring neurons (Smith et al. 2018; Dahmen et al. 2022). This implies that long-range recurrent connections are not necessary for generating highly synchronous activity in distant neurons and suggests moreover that heterogeneity in lateral connectivity may provide a backbone for the subsequent organization of long-range connections via activity-dependent Hebbian plasticity mechanisms.

DESYNCHRONIZATION AND SPARSIFICATION OF NEURAL ACTIVITY THROUGHOUT DEVELOPMENT

Spontaneous activity in the neocortex becomes progressively more desynchronized during development, giving way to an asynchronous activity state that forms the basis of information processing in adult circuits. In this state, individual neurons sustain higher firing rates on average (as opposed to the quiescence of early networks punctuated by infrequent bursts), but population activity is sparse, with fewer neurons active at any given time (Fig. 2A). Continuous low-amplitude oscillations replace network bursts observed in the LFP (Colonnese et al. 2010; Harris and Thiele 2011; Shen and Colonnese 2016), and the activity of neighboring neurons observed in Ca^{2+} imaging and electrophysiology strongly decorrelates (Golshani et al. 2009; Rochefort et al. 2009; Che et al. 2018; Chini et al. 2022). The gradual developmental strengthening of recurrent excitatory connections between pyramidal

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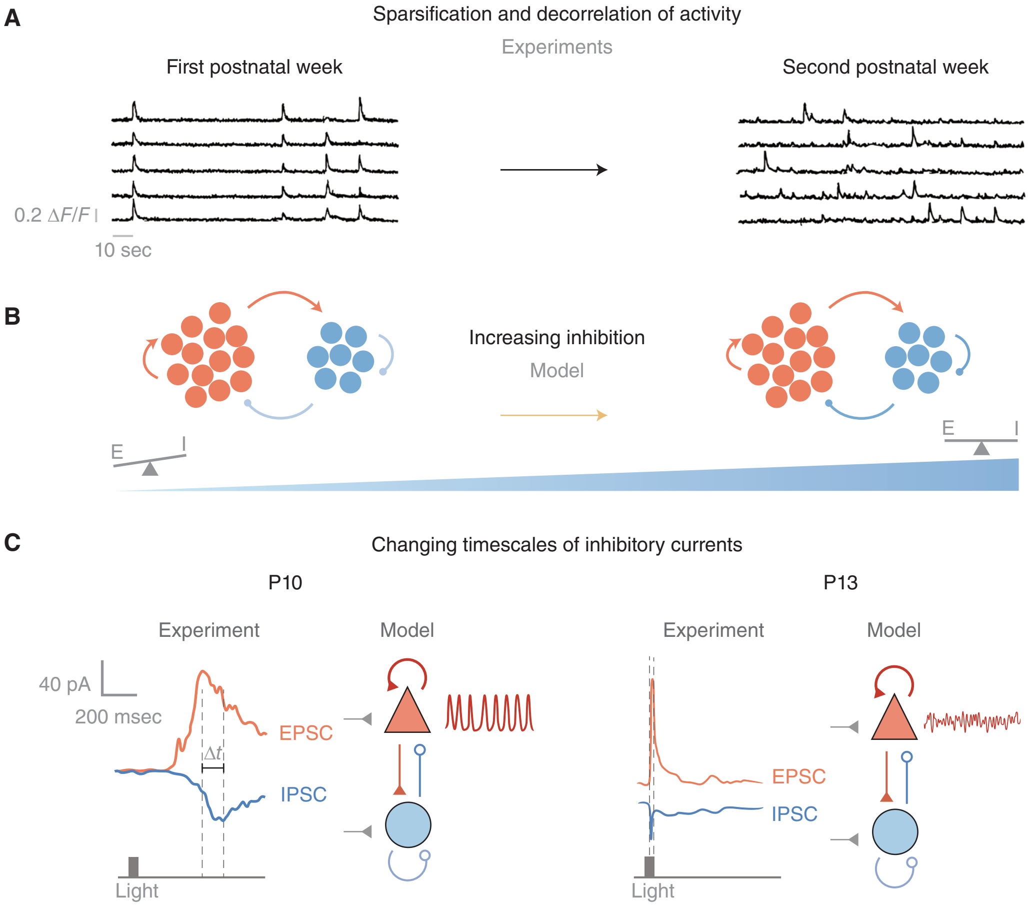

Figure 2. Mechanisms for sparsification of neural activity. (*A*) Network activity transitions from silent activity punctuated by synchronous network bursts to sparse, continuous, and decorrelated activity over the second postnatal week. (Based on data from Rochefort et al. 2009.) (*B*) A relative increase in inhibition through the strengthening of inhibitory synapses (Chini et al. 2022) or the increase in excitability of inhibitory interneurons (Maldonado et al. 2021) are plausible factors driving this transition. (*C*) Faster kinetics of inhibitory synaptic currents reduce the time delay between excitatory and inhibitory responses to perturbations, causing large network events to disappear. (Based on data from Romagnoni et al. 2020.)

neurons (Ko et al. 2013) likely facilitates the ability of cortical circuits to sustain persistent activity (Barak and Tsodyks 2007; Rahmati et al. 2017). The concurrent desynchronization and sparsification of such activity arise from multiple developmental changes occurring in parallel at the cellular and circuit levels. Recent modeling work has dissected the mechanisms underlying these developmental changes in spontaneous activity, including changes in the relative balance between excitation and inhibition, in single-neuron properties, and in connectivity patterns.

One factor driving the developmental desynchronization and sparsification of activity is the strong increase in the inhibitory influence of GABAergic interneurons. Across brain regions, the weak impact of inhibition at the cellular and network level at birth progressively increases over development (Fig. 2B). Throughout development, neurons receive a decreasing ratio of excitatory to inhibitory conductances across stimulus conditions until an approximate balance is reached by adulthood (Dorrn et al. 2010; Zhang et al. 2011). This strengthening of inhibition over development is driven by multiple factors, including the progressive migration and integration of interneurons into the cortex (Daw et al. 2007), an overall increase in the number and density of inhibitory synapses (Etherington and Williams 2011), the gradual shift in chloride reversal potential (Lazarus and Huang 2011), changes in active and passive membrane properties (Le Magueresse and Monyer 2013), and an acceleration of the kinetics of postsynaptic currents due to changing receptor subunit compositions (Pangratz-Fuehrer and Hestrin 2011).

Computational models elucidate how these diverse factors that increase inhibitory influence interact to produce developmental changes at the network level. For example, Rahmati et al. (2017) observed two notable developmental changes when mean-field models for spontaneous activity generation in the visual cortex were parameterized for later developmental stages (P10 and P20). First, synchronous network bursts became harder to generate, consistent with the experimentally observed disappearance of retinal wave–triggered spindle bursts by P14 (Murata and Colonnese 2016; Shen and Colonnese 2016). Second, new stable fixed points in the model arose at nonzero firing rates, indicating the capability of the network to sustain persistent activity states that can be metastable and have been implicated in different computational regimes of adult networks (Mazzucato et al. 2019; Stringer et al. 2019; Modol et al. 2020; Nakazawa et al. 2020). In the model, two factors drove the disappearance of network bursts: a strong increase in absolute inhibitory synaptic strength and a decrease in the efficacy of synaptic transmission by a change in excitatory short-term facilitation. Several other factors support the emergence of persistent activity states, including an increase in the activation thresholds in both excitatory and inhibitory populations and a speeding up of inhibitory short-term depression. Notably, many of the model parameters driving developmental changes in spontaneous activity boost the strength of inhibitory synaptic connections relative to excitatory. Hence, the model makes specific predictions for the role of each parameter, which could subsequently be tested in perturbation experiments that selectively manipulate each biological correlate (Rahmati et al. 2017).

In addition to inhibitory strengths, the timing of inhibition relative to excitation could also be an important factor behind the developmental sparsification in network dynamics. In the rodent visual cortex, the delay between the peaks of light-evoked inhibitory and excitatory postsynaptic currents decreases substantially between P10 and P13 shortly before eye opening (Fig. 2C), suggesting that inhibition speeds up fractionally faster than excitation (Colonnese 2014). In a different mean-field excitatory–inhibitory model, this change in delay was found to be the key parameter driving a switch from oscillatory to stable dynamics that matches activity changes observed in vivo during development (Romagnoni et al. 2020). Several biophysical factors could underlie the faster kinetics of inhibitory currents, including the progressive integration of fast-spiking PV-expressing interneurons into the cortex (Colonnese 2014; Modol et al. 2020) or the rearrangements in thalamocortical input to interneuron subtypes (Daw et al. 2007; Marques-Smith et al. 2016; Tuncdemir et al. 2016; Guan et al. 2017). In the model, the transition could occur even in the absence of changes in feedforward input, suggesting that increased thalamic input is a complementary but not necessary component of the switch (Romagnoni et al. 2020).

Beyond the mean-field models that average activity across individual neurons, increasing the net strength of inhibition in large spiking networks of excitatory and inhibitory neurons also leads to sparser firing with reduced pairwise spike correlations between neurons (Chini et al. 2022). This result recapitulates the sparsification occurring in the first two postnatal weeks and also when optogenetically stimulating inhibitory neurons in the prefrontal cortex in vivo (Chini et al. 2022). Decorrelation of neuronal activity due to increased inhibition has also been observed in the mouse primary visual cortex upon application of the neuromodulator oxytocin, which increases the excitability of SST interneurons, and was also captured in a large spiking network (Maldonado et al. 2021). Therefore, despite the distinct manner of increasing net inhibition in each case—by increasing the ratio of inhibitory and excitatory conductances (Chini et al. 2022) or by increasing the resting membrane potential of a subset of inhibitory neurons (Maldonado et al. 2021)—the similar influence on network decorrelation and sparsification points to the robustness of the proposed mechanism.

Interestingly, although the period of sparsification coincides with the onset of sensory experience, the sparsification process is largely independent of sensory inputs, and sensory deprivation has little effect on the sparsification of neural activity (Golshani et al. 2009; Rochefort et al. 2009). In line with this, spontaneous activity drives activity-dependent changes in network connectivity that may also support the sparsification of spontaneous activity observed in the cortex. Although feedforward thalamocortical connections in sensory pathways are initially diffuse and imprecise, activity-dependent synaptic plasticity can use developmental spontaneous activity to refine them into specific topographic projections over the first postnatal weeks of rodent life (Ackman and Crair 2014; Richter and Gjorgjieva 2017; Thompson et al. 2017). A network model for this type of refinement can lead to cortical activity in which network bursts downstream from the sensory periphery occur more rarely and recruit fewer neurons, reminiscent of sparsification (Wosniack et al. 2021).

Alongside the developmental increase in inhibition and refinement of network connectivity, changes in biophysical single-neuron properties may also contribute to changes in synchronization between neuronal populations. A developmental increase in the ratio of sodium to potassium conductances can endow single neurons with the property of gain scaling as they mature, which allows them to respond adaptively to the amplitude of stimuli encountered (Mease et al. 2013). Modeling work has shown that the absence of gain scaling at birth can allow peripheral spontaneous activity to be propagated across many downstream layers in the form of synchronous bursts. As single-neuron gain scaling emerges over the first postnatal week, network responses become graded and less synchronous and recruit fewer cells at any given time, also reminiscent of sparsification (Gjorgjieva et al. 2014).

In summary, computational models have provided unique insights into both the generation of synchronous network bursts prevalent in the early postnatal brain and the transition to sustained, continuous, and decorrelated activity that takes place over subsequent phases of development. By capturing transitions between dynamical regimes, models have been especially informative in understanding the impact of cellular and synaptic parameters, either by extracting such parameters from experiments (Rahmati et al. 2017) or by deriving them based on target features of activity (Romagnoni et al. 2020). The latter approach can be used to ultimately derive a specific developmental parameter trajectory that recapitulates in vivo activity patterns, thus forming predictions that can be tested experimentally.

ACTIVITY-DEPENDENT REFINEMENT OF CONNECTIVITY THROUGH SYNAPTIC PLASTICITY

As spontaneous activity patterns evolve during development, they play a crucial role in setting up structured connectivity in developing neural circuits. Emerging evidence suggests that activity-dependent synaptic plasticity mechanisms use the synchronized and wave-like activity patterns generated in developing circuits to establish the connectivity required for sensory processing and behavior in mature circuits. In sensory cortices in particular, two types of connectivity have typically been the subject of experimental and theoretical work. The first is the establishment of receptive fields at the single-neuron level, defined as the set of inputs to the neuron that gives rise to its response properties (Fig. 3A). These receptive fields refine during development by reducing the number of inputs (Chen and Regehr 2000; Thompson et al. 2017) and often (but not always) represent the neuron's tuning to a particular feature of the sensory input—for example, the orientation of an object in the visual cortex or tone frequency in the auditory cortex (Hubel and Wiesel 1962; Knudsen and Konishi 1978; Clopath et al. 2010; Gjorgjieva et al. 2011; Vogels et al. 2011). The second is the emergence of

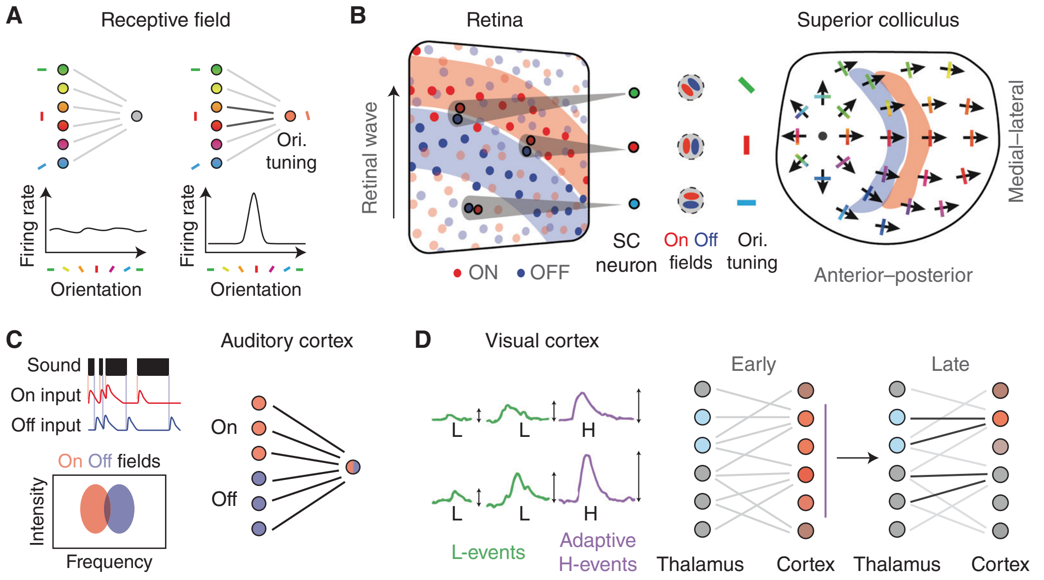

Figure 3. Spontaneous activity-driven refinement of feedforward connections. (*A*) The emergence of a receptive field in a postsynaptic neuron by the selective refinement of multiple presynaptic inputs. Line thickness indicates synaptic strength. (*B*) Stage III waves in the retina that asynchronously activate ON (red) and OFF (blue) retinal ganglion cells (Kerschensteiner and Wong 2008) can generate receptive fields in the superior colliculus consisting of separate but adjacent ON and OFF subfields, leading to orientation selectivity. Note that here orientation selectivity is directly represented by the composition of the receptive field and not only by the firing rate of the neuron due to the inputs it receives, as in *A*. The directional bias of stage III waves generates the concentric orientation map in the superior colliculus. (Schematic adapted from Teh et al. 2023.) (*C*) Natural auditory stimuli invoke alternating responses to sound onset (ON) and offset (OFF) (*upper left*). In a model of ON and OFF inputs to an auditory cortex neuron (*right*), this leads to a separation of ON and OFF subfields at adjacent frequencies (*lower left*) as seen in the adult. (Schematic adapted from Sollini et al. 2018.) (*D*) Modeling the role of spontaneous low-synchronicity (L) events and high-synchronicity (H) events in the visual cortex on the refinement of thalamocortical connectivity. L-events refine receptive fields in the cortex by strengthening the connections to fewer thalamocortical inputs, generating topographic connectivity, which preserves neighboring relations between the thalamus and the cortex. H-events adaptively regulate their amplitude to homeostatically regulate synaptic strength. (Schematic adapted from Wosniack et al. 2021.)

organized feedforward connectivity (typically called a map) between neuronal populations, one defined as an input and the other as a target projection area. In most sensory systems, these connectivity maps are topographically organized, whereby stimulus features in the input area (e.g., the sensory periphery) are represented in downstream areas (e.g., the cortex) in a manner that preserves neighboring relations. For instance, the map between the retina and downstream visual areas—such as the dorsal lateral geniculate nucleus (dLGN) of the thalamus, the superior colliculus, and the primary visual cortex—is known as a retinotopic map (Schuett et al. 2002; Mrsic-Flogel et al. 2005; Piscopo et al. 2013). Similar topographic maps exist in the somatosensory and auditory systems (Garrett et al. 2014; Mizuno et al. 2018; Antón-Bolaños et al. 2019; Kersbergen et al. 2022). Here, we review theoretical and modeling frameworks inspired by extensive experimental evidence of the multiple ways in which spatiotemporal correlations in early peripheral activity can set up receptive fields and establish topographic connectivity (Cang and Feldheim 2013; Kirkby et al. 2013; Richter and Gjorgjieva 2017). Refined feedforward connectivity influences and interacts with downstream network activity patterns in a manner that ultimately shapes local recurrent connectivity and, indirectly, top-down modulatory feedback (Murakami et al. 2022). We also review recent theoretical work studying how local network dynamics instruct the formation of appropriate recurrent connections (Ko et al. 2013; Kim et al. 2020). The emerging picture is that of feedforward and recurrent connections becoming gradually aligned with each other, which is beneficial for the amplification and stabilization of sensory-evoked responses following early development (Lempel and Fitzpatrick 2023).

The phenomenological description of activity-dependent plasticity mechanisms that are used to translate correlated activity patterns into synaptic connectivity changes are known as learning rules. Most of these learning rules are based on the Hebbian principle that coincident pre- and postsynaptic activity potentiates synaptic weights (Hebb 1949) but can depend on different aspects of neural activity, including firing rates, spike timing, voltage, and calcium (Bi and Poo 1998; Abbott and Nelson 2000; Song et al. 2000; Clopath et al. 2010; Graupner and Brunel 2012; Magee and Grienberger 2020). Their exact dependence varies across brain regions, species, neuron type, and developmental age (Turrigiano and Nelson 2004; Lohmann and Kessels 2014). Most experimental studies characterizing spontaneous activity in development have found much slower correlation timescales than the corresponding correlation timescales in adult activity, raising questions about the nature of the activity-dependent learning rules using this activity (Butts et al. 2007; Colonnese and Khazipov 2010; Winnubst et al. 2015). For instance, retinal waves have burst durations of ~1 sec (Meister et al. 1991; Wong et al. 1993; Ackman et al. 2012) and transmit information at a timescale of 1–2 sec (Butts and Rokhsar 2001). Therefore, several models have demonstrated that the activity-dependent plasticity rules that interpret developmental spontaneous activity patterns into connectivity must be operating on similar timescales (Butts et al. 2007; Gjorgjieva et al. 2009; Bennett and Bair 2015; Winnubst et al. 2015). Below we review these models according to the type of connectivity they investigate.

EMERGENCE AND REFINEMENT OF STRUCTURED FEEDFORWARD CONNECTIVITY

Locally correlated activity patterns that activate a few neighboring neurons are ideally poised to establish topographic feedforward connectivity and refine sensory receptive fields. Classical theoretical studies explained how Hebbian plasticity in rate-based models can instruct topographic map formation in feedforward connections using locally correlated activity (Hebb 1949; Miller and MacKay 1994; Richter and Gjorgjieva 2017). However, more recent work has provided extensive new evidence about the nature of correlated activity and the type of activity-dependent plasticity rules adapted to this activity.

Activity-based connectivity refinement is best understood in the visual system, where the structure of the driving input from the sensory periphery has been extensively characterized. For instance, retinal waves provide a source of correlated activity that drives the segregation of retinotopically organized inputs into distinct regions in the thalamus and visual cortex, leading to the formation of the retinotopic map between the retina and thalamus, as well as thalamus and visual cortex (Kirkby et al. 2013; Ko et al. 2013; Ackman and Crair 2014; Thompson et al. 2017). Because retinal waves consist of bursts, phenomenological learning rules that depend on bursts have been proposed to instruct receptive field formation and refinement (Butts et al. 2007; Gjorgjieva et al. 2009). Even when using spike-timing-dependent plasticity (STDP), modeling work has shown that the time constant of STDP should be matched to retinal wave speed to set the spatial scale of emergent connectivity and receptive field size (Bennett and Bair 2015). Biologically, this matching of timescales between plasticity rules and spontaneous activity correlations could be attributed to development-specific synaptic properties, such as a shift in the receptor composition of *N*-methyl-D-aspartate (NMDA) receptors (Liu and Chen 2008) or the dominance of slower NMDA over faster α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Tikidji-Hamburyan et al. 2023). Recent modeling work found that such dominance is necessary to prevent initial unrefined connections from the retina to thalamic neurons from generating misinformative, so-called "parasitic" correlations at fast timescales, which could misguide connectivity refinement driven by plasticity and limit the transmission of spatially informative input correlations at slower timescales (Tikidji-Hamburyan et al. 2023).

With the developmental modification of spontaneous activity properties, the properties of the receptive fields and maps driven by this activity through synaptic plasticity also evolve. As developmental spontaneous activity is localized in space and time, more precise temporal correlations begin refining finer receptive field aspects, including their segregation into separate subfields. By providing simulated stage III retinal waves as input to a feedforward rate network with Hebbian plasticity, Teh et al. (2023) studied how specific temporal correlations in these waves affect the organization of receptive fields in the superior colliculus. In particular, the unique firing during stage III retinal waves where ON retinal ganglion cells precede the firing of OFF retinal ganglion cells (Kerschensteiner and Wong 2008) was found to guide the emergence of orientation tuning of individual collicular cells by generating aligned ON and OFF subfields (Fig. 3B, left). Additionally, modeling spatiotemporal correlations of retinal waves supported the formation of the orientation preference map as in the mouse superior colliculus, whereas introducing a propagation bias as found at the transition of stage II to stage III waves induced a concentric organization of orientation tuning and aligned the center of the orientation map to the center of vision (Fig. 3B). This extends previous modeling work that has found that temporally delayed inputs can generate direction selectivity in feedforward networks, either through lagged input channels (Blais et al. 2000) or delayed inhibitory activity (Gjorgjieva et al. 2011) in single neurons by considering neuronal populations organized in space.

In some sensory systems, as the activity transitions from spontaneous to sensory-evoked, the temporal correlations of evoked patterns acquire properties appropriate to induce subfield segregation. In the auditory system, Sollini et al. (2018) showed that the natural alteration of sound onset and offset present in environmental sounds, combined with Hebbian plasticity, is sufficient to gradually segregate ON and OFF receptive fields of neurons in the mouse auditory cortex, which are located at adjacent but nonoverlapping frequencies by adulthood (Fig. 3C; Sollini et al. 2018). This result implies that the statistical structure of natural stimuli in the external world can be well-suited to continue the process of receptive field refinement initialized by spontaneous activity. This is supported by experiments in the mouse and ferret visual cortex showing that sensory experience after eye opening further refines connectivity (Ko et al. 2013) and sets up direction tuning (Li et al. 2006; Chang et al. 2020) following the emergence of orientation-tuned receptive fields without evoked visual input (White et al. 2001).

Once retinal waves propagate to the visual cortex, they invoke spontaneous LFP spindle bursts and local calcium events, which continue to shape connectivity in local circuits (Hanganu et al. 2006; Colonnese and Khazipov 2010). Modeling work has shown that the local, low-synchronicity calcium events triggered by retinal waves are sufficient to establish thalamocortical receptive fields in a feedforward rate-based network via Hebbian plasticity (Fig. 3D; Wosniack et al. 2021). In contrast, the global, high-synchronicity events that simultaneously activate larger neural populations were found to adapt to ongoing activity in the network and thus homeostatically regulate connection strength (Wosniack et al. 2021).

Simultaneous to the development of experimental approaches to study activity and plasticity at the cellular and network level, methods now allow us to investigate the subcellular or synaptic organization during early postnatal development (Kleindienst et al. 2011; Takahashi et al. 2012). Multiple studies have revealed that already early in development and before the onset of sensory experience, synapses organize on individual dendritic branches in synaptic clusters, highly correlated groups of synapses near each other in dendritic space (Kleindienst et al. 2011; Takahashi et al. 2012; Leighton et al. 2023). Kirchner and Gjorgjieva built a model for synaptic cluster formation based on experimentally identified interacting neurotrophic molecules directly implicated in the developmental emergence of functional clusters in the visual cortex before eye opening (Niculescu et al. 2018; Kirchner and Gjorgjieva 2021). Beyond capturing the emergence of functional clusters driven by spontaneous activity during development, the model could also relate them to the synaptic clusters in the adult based on their representation of specific stimulus features. Interestingly, by including species-specific differences such as the amplification factor of visual space (modeled by the receptive field spread), the model could infer clustering in different species with respect to different sensory features, including orientation selectivity in ferrets (Wilson et al. 2016) and receptive field overlap in mice (Iacaruso et al. 2017), shedding light on how interspecies differences emerge during development.

Taken together, these computational models at the subcellular, cellular, and network levels make concrete proposals for the role of developmental patterns of spontaneous activity in shaping organization at different scales. A common emerging theme is the gradual refinement occurring simultaneously with the evolution of activity patterns, with coarser receptive fields and maps forming early on, and more refined features emerging later in development with the onset of sensory experience. Most models rely on forms of Hebbian synaptic plasticity that use slower developmental timescales to instruct this refinement.

EMERGENCE AND REFINEMENT OF STRUCTURED RECURRENT CONNECTIVITY

Many adult computations rely on the structured recurrent connectivity that emerges in development concurrently with feedforward connectivity through activity-dependent plasticity to ultimately shape the highly structured microcircuits and networks that underlie adult sensory processing. In the sensory cortex, a key connectivity feature that emerges shortly after eye opening is strong bidirectional connections between neurons with similar tuning properties (Ko et al. 2013; Kim et al. 2020; Crodelle and McLaughlin 2021). Using multistage spiking network simulations, Ko et al. (2013) investigated the sequential development of connectivity in the visual cortex. Their model showed that first, early gap-junction coupling facilitates the activity-dependent refinement of structured feedforward synaptic connections. Next, strong bidirectional connections develop among similarly tuned cortical neurons, forming functional subnetworks organized into so-called assemblies (Fig. 4A). Notably, allowing recurrent and feedforward connections to be simultaneously plastic produced short-lived biases in recurrent connectivity and corrupted the establishment of feedforward receptive fields. These modeling results support the notion that recurrent connections refine after feedforward connections are appropriately formed. In contrast, however, driving recurrent neural network models with inputs emulating natural image statistics or allowing the models to implement a richer set of biologically plausible activity-dependent synaptic plasticity can allow feedforward receptive fields and recurrent assembly structure to emerge through synaptic plasticity simultaneously (Miconi et al. 2016; Eckmann et al. 2023). These modeling efforts lead to the conclusion that input correlations in natural images or other visually structured input may provide a powerful instruction for the simultaneous feedforward or recurrent connectivity organization, or that an appropriate synergy of synaptic plasticity mechanisms may operate at each pathway. Although these models involve more parameters than previously discussed mean-field models, they also allow analytical treatment under certain assumptions (Eckmann et al. 2023). A recent modeling study suggested that bidirectional recurrent connectivity could also arise through spontaneous activity before eye opening in species with orientation maps (Kim et al. 2020). Modeling stage III retinal waves using retinal ganglion cell mosaics measured in cats and monkeys produced the coactivation of V1 network neurons with similar tuning and induced horizontal connections between neurons with shared orientation preference (Fig. 4B; Kim et al. 2020). After the establishment of recurrent connections, the authors observed that the spontaneous network activity correlates with the underlying orientation map, as experimen-

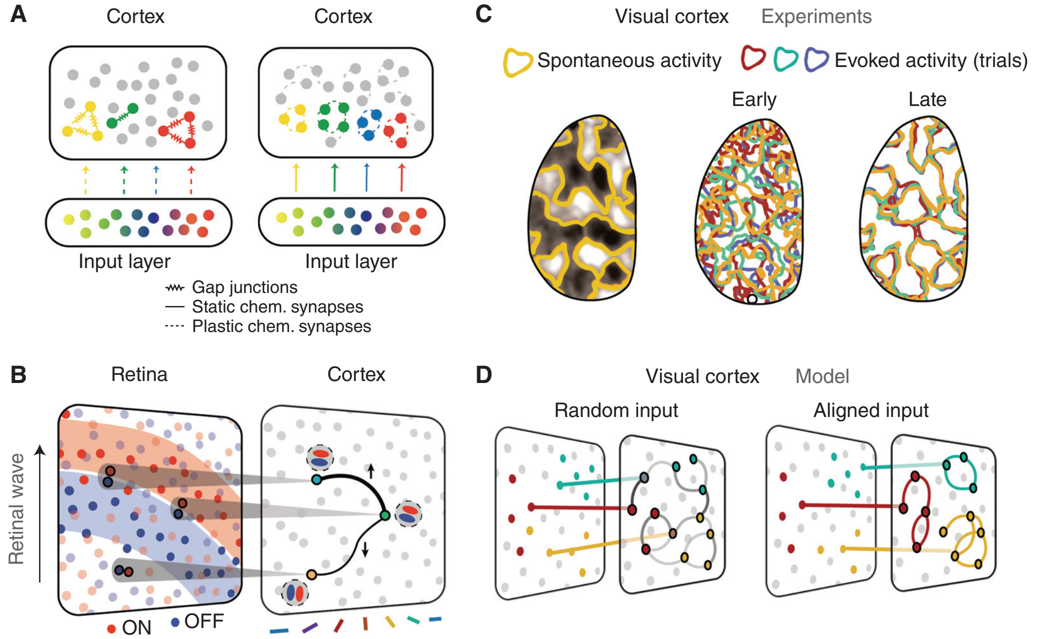

Figure 4. The interaction between the plasticity of feedforward and recurrent connectivity. (*A*) Gap-junction-connected neurons acquire similar feedforward receptive fields (*left*). Feedforward input can induce bidirectional recurrent connections between neurons with similar tuning (*right*). (Schematic adapted from Ko et al. 2013.) (*B*) Stage III retinal waves can also induce bidirectional recurrent connections between similarly tuned neurons in the visual cortex. (Schematic adapted from Kim et al. 2020.) (*C*) Evoked and spontaneous activity in the ferret visual cortex change over sensory experience; both become more similar to each other, and evoked activity becomes more stable over trials. (Schematic adapted from Trägenap et al. 2023.) (*D*) Alignment between feedforward inputs and recurrent connectivity is proposed to cause the changes in network activity over sensory experience shown in *C*. (Schematic based on data in Trägenap et al. 2023.)

tally observed in cats and ferrets (Kenet et al. 2003; Smith et al. 2018).

Such organization of recurrent connections has been framed as a process of feedforward-recurrent alignment, in which activity generated by feedforward connections becomes progressively more aligned to the activity generated spontaneously by the recurrent cortical network (Fig. 4D; Trägenap et al. 2023; see also Fiser et al. 2010 for a related proposal). Experimental work in the ferret visual cortex has shown that, although visually evoked activity before eye opening (by temporarily forcing the eyes open) is highly variable, it gradually becomes more reliable with visual experience (Fig. 4C; Trägenap et al. 2023; see also Avitan et al. 2021; Avitan and Stringer 2022). The authors confirmed with a phenomenological model that the progressive alignment of feedforward and recurrent connections underlies the observed change in network activity. In a rate-based recurrent network model, the authors generated feedforward input patterns with varying degrees of alignment to the recurrent connectivity. They showed that as alignment increases, visually evoked responses and spontaneous activity change and become more similar to each other as the network selectively amplifies the aligned components of the feedforward input patterns (Fig. 4D). These results highlight that feedforward and recurrent connections may become more aligned throughout development and lead to more reliable sensory representations, thus preparing the cortical circuit for mature sensory processing. Recent experimental work in the ferret visual cortex has confirmed this hypothesis by focusing on the connectivity supporting orientation selectivity from layer 4 to layer 2/3 as well as recurrent connectivity within layer 2/3 (Lempel and Fitzpatrick 2023). Future theoretical and experimental work could examine whether refinement through plasticity and sensory inputs indeed causes this gradual alignment between feedforward and recurrent connections.

INHIBITORY CONTROL OF PLASTICITY AND EMERGENT CONNECTIVITY

As neural circuits in the developing brain generate and are refined by spontaneous and early sensory activity, there must be safety checks in place to prevent excessive excitation and ensure stable activity levels. This control is mainly achieved by inhibition, which must be appropriately incorporated to prevent epileptic activity as developing neurons and synapses acquire mature ion channel composition and synaptic transmission abilities (as discussed in the section Desynchronization and Sparsification of Neural Activity throughout Development). Synaptic plasticity at inhibitory synapses could be an additional factor underlying the developmental strengthening of inhibition. Alongside promoting spontaneous activity sparsification (Golshani et al. 2009; Larisch et al. 2021; Chini et al. 2022), inhibition and inhibitory plasticity affect multiple properties of developing networks, including the gradual emergence of excitation/inhibition (E/I) balance (Froemke 2015), controlling neuronal firing properties (Gjorgjieva et al. 2014; Avitan and Goodhill 2018; Glanz et al. 2021; Jia et al. 2022; Trägenap et al. 2023), and regulating excitatory plasticity (Agnes et al. 2020; Miehl and Gjorgjieva 2022). E/I balance typically refers to the coregulation of excitation and inhibition as measured by the ratio of excitatory and inhibitory neuronal inputs (Froemke 2015; Hennequin et al. 2017). E/I balance can occur in multiple forms at the population, single-neuron, and dendritic level and at a range of timescales, with different computational implications for circuit processing (Dorrn et al. 2010; House et al. 2011; Barnes et al. 2015; Field et al. 2020; Wu et al. 2022). Various inhibitory plasticity rules have been proposed to regulate E/I balance in computational models, often in conjunction with excitatory plasticity (Vogels et al. 2011; Luz and Shamir 2012; Kleberg et al. 2014; Wu et al. 2022). As with the activity-dependent refinement of excitatory connectivity, the coordinated interaction of excitatory and inhibitory plasticity is typically studied in models with feedforward connectivity, which include the emergence of sensory receptive fields (Vogels et al. 2011; Clopath et al. 2016; Miehl and Gjorgjieva 2022), place fields (Weber and Sprekeler 2018), and grid fields (Weber and Sprekeler 2018) in a single postsynaptic neuron based on input statistics (Luz and Shamir 2012; Kleberg et al. 2014; Agnes et al. 2020). In recurrent circuits, inhibitory plasticity also shapes strongly connected cells such as neuronal assemblies (Litwin-Kumar et al. 2017; Miehl and Gjorgjieva 2022) and chain-like structures (Zhang et al. 2014; Maes et al. 2020), as well as ensures tuning diversity and efficient sensory representation (Larisch et al. 2021).

However, the delayed emergence of inhibitory long-term plasticity may be insufficient to establish E/I balance early on in development (Dorrn et al. 2010). One proposal for achieving stable firing in the absence of early developmental E/I balance is STP (Jia et al. 2022), which was already shown to play a role in generating spontaneous activity (Rahmati et al. 2017). In a feedforward model, Jia et al. (2022) proposed that short-term depression at excitatory synapses can stabilize neural activity in very young animals when inhibition is immature. As inhibition strengthens, the model supports the switch of STP at excitatory synapses from depression to facilitation (Reyes and Sakmann 1999). This switch stabilizes activity and supports E/I cotuning and the emergence of temporally precise spiking in the model. This is similar to the finding by Rahmati et al. (2017) that faster recovery from excitatory short-term depression supports the transition from synchronous to decorrelated spontaneous activity. These results underscore the need to simultaneously consider different forms of synaptic plasticity that underlie activity-dependent changes in connectivity.

Inhibitory neurons can be divided into multiple distinct subtypes based on their electrophysiological, morphological, and transcriptomic properties (Tremblay et al. 2016). Computational models have benefited from multiple experimental studies of interneuron-specific plasticity and explored its role in feedforward and recurrent networks (Wilmes et al. 2016; Agnes et al. 2020; Wu et al. 2022; Agnes and Vogels 2024; Lagzi and Fairhall 2024). As understanding how inhibition matures developmentally is proving crucial for understanding circuit development, new models need to consider this inhibitory diversity in setting up mature circuits. This includes, for instance, the study of transient circuits where SST interneurons are integrated before PV (Daw et al. 2007; Marques-Smith et al. 2016; Tuncdemir et al. 2016; Guan et al. 2017). Moreover, increasing knowledge of the different short-term dynamics of interneuron subtypes (Campagnola et al. 2022) and their different targeting biases onto pyramidal cells (Jiang et al. 2015) all point toward diverse and understudied influences on developing network dynamics and plasticity.

CONCLUSIONS AND OUTLOOK

Development is a dynamic process in which multiple mechanisms coordinate to establish the single neuron, synaptic, and network properties of adult neuronal circuits. Here, we reviewed the types of early developmental spontaneous and sensory-evoked activity and their interaction with synaptic plasticity to shape network connectivity and function. We focused on mechanistic models at different levels of abstraction, constrained by experimental data, which explore the components underlying spontaneous activity generation and activity-dependent organization. These models reveal nontrivial interactions between excitation, inhibition, changing connectivity, and ongoing activity that weave together to guide brain development.

Despite this progress, many open challenges remain. One question concerns the dynamical regime of immature networks. In the adult, experimental evidence suggests that cortical regions operate in the inhibition-stabilized regime, where strong recurrent excitatory connectivity requires strong recurrent inhibition to stabilize activity, with ample implications for information processing (Ozeki et al. 2009; Adesnik 2017; Kato et al. 2017; Sanzeni et al. 2020; Sadeh and Clopath 2021). However, at what stage networks become inhibition-stabilized during development is unclear. On one hand, low connection density between excitatory pyramidal cells, the delayed integration of inhibitory interneurons, and the gradual strengthening of inhibition measured in the rodent neocortex suggest that cortical networks may not yet operate as an inhibition-stabilized network during the first postnatal weeks. Certain theoretical work presented in this review supports this idea, finding that networks modeled early on (∼P3–P10) are intrinsically stable and that the inhibition-stabilized regime emerges and becomes accessible as development progresses (Rahmati et al. 2017; Graf et al. 2022; Kirmse and Zhang 2022). However, we also reported work supporting an inhibitory role of GABA already by P2 that, combined with theoretical modeling, suggests that recurrent networks in the PFC may operate in the inhibition-stabilized regime shortly after birth (Chini et al. 2022).

A second challenge concerns the extent to which simultaneously developing neural circuits interact. The developing brain assembles into a hierarchical circuit with extensive inter- and intraregion connections (Murakami et al. 2022). In recent years, experiments have begun to understand the crucial role of feedback connectivity in adult animals for various computations such as predictive coding and context modulation (Marques et al. 2018; Morimoto et al. 2021). This leads to the question of how feedback connectivity affects spontaneous activity and connectivity refinement in postnatal development. Some experimental work has implicated corticothalamic feedback in the generation of spontaneous spindle bursts in the cortex in the first two postnatal weeks (Murata and Colonnese 2016). A computational study has further proposed that, in the second postnatal week, feedback connections are optimized to prevent misinformative correlations (Tikidji-Hamburyan et al. 2023). However, a complete understanding of the emergence of structured feedback connectivity and its interaction with spontaneous activity needs further experimental and computational research.

A third challenge concerns the generalizability of models constrained by experimental data from sensory cortices to other brain regions. Several kinds of spontaneous activity patterns are observed in the hippocampus, but their role in the generation of different hippocampal representations of space (head direction cells, grid cells, place cells) that emerge at different developmental time points remains unclear (Langston et al. 2010; Wills et al. 2010; Wills and Cacucci 2014; Tan et al. 2017). Similarly, the propagation of activity and refinement of connectivity between the hippocampus, olfactory, and prefrontal cortex (Gretenkord et al. 2019; Chini and Hanganu-Opatz 2021; Xu et al. 2021) remains a rich avenue for further theoretical and experimental research.

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