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Plasticity and specificity of cortical processing networks

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The cerebral cortex is subdivided into discrete functional areas that are defined by specific properties, including the presence of different cell types, molecular expression patterns, microcircuitry and long-range connectivity. These properties enable different areas of cortex to carry out distinct functions. Emerging data argue that the particular structure and identity of cortical areas derives not only from specific inputs but also from unique processing networks. The aim of this review is to summarize current information on the interplay of intrinsic molecular cues with activity patterns that are driven by sensory experience and shape cortical networks as they develop, emphasizing synaptic connections in networks that process vision. This review is part of the *TINS* special issue on *The Neural Substrates of Cognition*.

Introduction

The function of the cerebral cortex relies on the development and plasticity of specific networks that process information. We will discuss recent studies of the structural and molecular mechanisms that underlie rapid activity-dependent plasticity of eye-specific inputs to the visual cortex during development – these studies employ a loss-of-function approach that reduces the drive from one or both eyes by visual deprivation. Important lessons also come from a novel model system that utilizes a gain-of-function approach for studying the role of activity: the rewiring of visual inputs to the auditory thalamus in neonatal animals to provide visual drive to the auditory cortex through development. Recent developments in imaging technologies for monitoring the structure and function of microcircuits *in vivo* have given us tremendous insights into the effects of sensory stimulation on cortical development. At the same time, molecular techniques are giving us increased understanding of both the intrinsic and the activity-dependent cues present in developing cortex.

Molecular determinants of visual pathways

Long-range pathways in the brain, including visual projections from the eyes to the thalamus and from the thalamus to the cortex, are specified by a host of molecules [1]. Evidence from the developing visual system and from other systems indicates that particular molecules regulate each of the stages of pathway development, including axon outgrowth, pathfinding, target recognition and arbor elaboration [2]. Furthermore, a scaffold of cell-specific connections along pathways and within targets is probably also laid down by molecular cues early in development [3].

Cortical arealization starts with signaling centers in the embryonic cortical mantle that lead to gradients of transcription factors early in development. The resulting expression patterns are likely to be responsible for cortical pathways and the setting up of area-specific connectivity, including inputs from visual thalamic nuclei to the visual cortex [2]. The visual cortex is a highly ordered structure where specific response properties are created, and in which neurons that have similar response properties are grouped together to form orderly representations of features such as ocular dominance, orientation preference and spatial frequency preference, overlaid on a map of retinotopy [4,5]. Within the visual cortex, several aspects of thalamocortical connections, including projections from eye-specific thalamic layers (which lay the basis for ocular-dominance columns) are established before the onset of visual activity [6,7]. Removing one or both retinas does not immediately disrupt eye-specific thalamocortical projections [8], implicating intrinsic, activity-independent cues in the targeting of these projections. EphA–ephrin-A signaling has a role in the guidance of visual thalamocortical axons and cortical patterning: altering the ephrin-A gradient in cortex alters the location and size of visual cortical areas [9,10]. Recent evidence in the somatosensory cortex indicates that thalamocortical and intracortical axons exhibit different modes of extension, further suggesting that mechanisms of axonal growth might depend on the cell type or on local molecular cues [11].

The presence of spontaneous locally correlated activity in the developing retina suggests that neural activity generated intrinsically in the developing brain might also be involved in setting up visual cortex connectivity. Indeed, disrupting this activity genetically or pharmacologically causes defects in cortical retinotopy [12]. At later stages of development, and particularly after

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eye-opening, visually driven activity has the potential to influence visual cortical connections significantly.

Activity-dependent changes during a critical period of development

Much work has been focused on a specific period of postnatal visual cortex development called the critical period for binocular plasticity, when visual activity can remodel cortical structure and function related to inputs from the two eyes (Figure 1a), and disruptions of binocularity lead to alterations in eye-specific connections in the cortex [13]. Although there are almost certainly other sensitive periods for other kinds of plasticity, during this period changes in the response properties of neurons in the visual cortex occur rapidly after closure of one eye, such that responses of the open eye become stronger while those of the deprived eye weaken. These changes can occur in the extragranular layers as rapidly as a few hours following deprivation [14–16]. Changes in response properties probably rely on changes in synaptic weights of connections serving the open and closed eyes, through potentiation and depression of the appropriate synapses [17]. Ocular-dominance plasticity serves as a key model system for examining the role of electrical activity in shaping the functional and structural changes that match cortical networks to their inputs.

Functional changes are tied to changes in postsynaptic structure

Functional changes at synapses elicited by plasticity are thought to be consolidated by structural changes in synapses and connectivity. In fact, both presynaptic and postsynaptic structures have stereotyped morphologies that are thought to enable them to function as synaptic compartments. The dendritic spine (Figure 1b), which is the postsynaptic structure of the vast majority of excitatory synapses in the cortex, has a unique morphology that enables Ca^{2+} compartmentalization

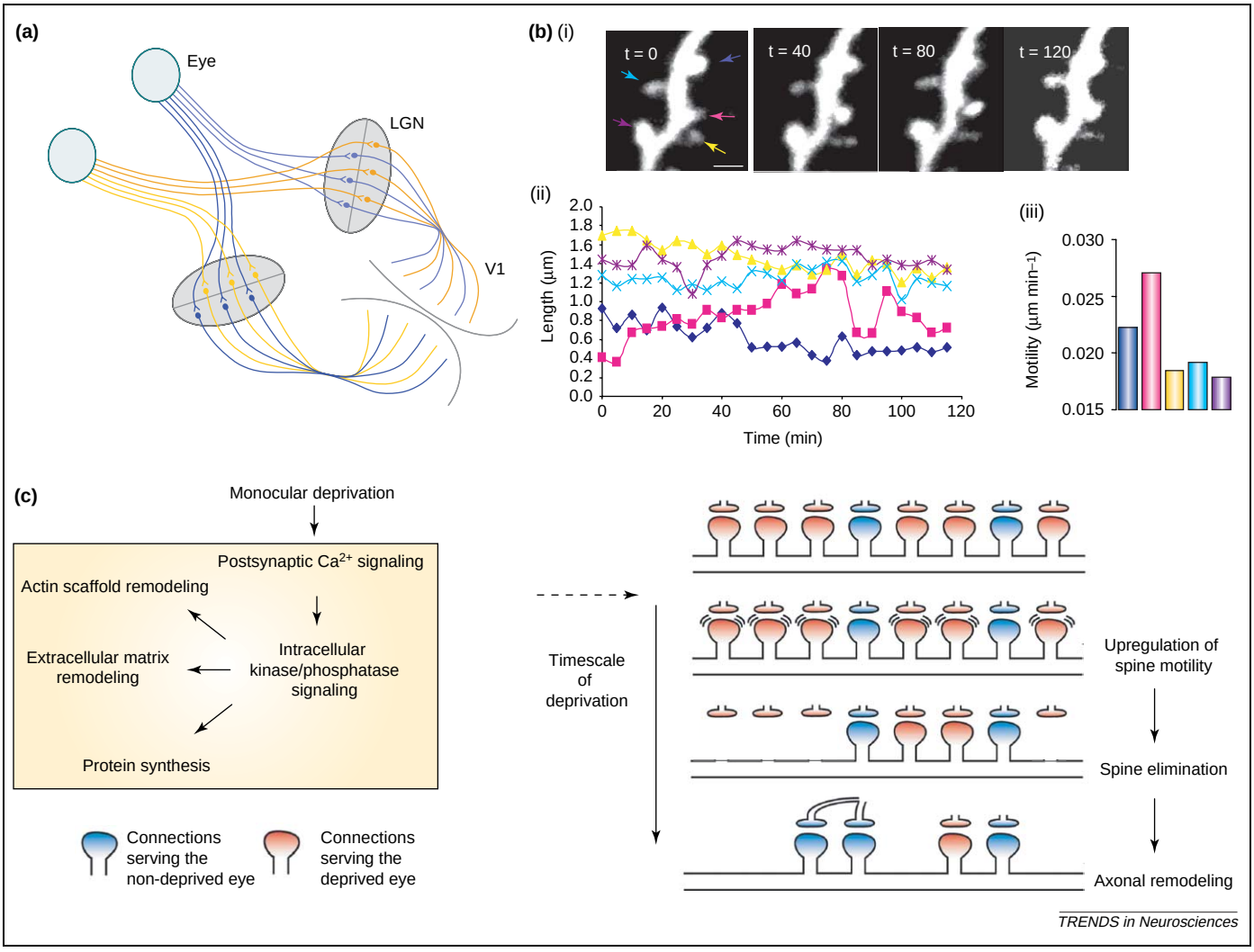

Figure 1. Visual deprivation as a model for studying activity-dependent plasticity of visual cortex. **(a)** Axons from the eyes project to the lateral geniculate nucleus (LGN) of the visual thalamus and subsequently to the primary visual cortex (V1). **(b)** Dendritic spines in the primary visual cortex *in vivo* are structurally plastic. Spine motility is heterogeneous, with motile spines (pink and dark blue arrows) located near stable spines (light blue, yellow and burgundy arrows) (i). Scale bar, 1 μm. Repeated measurements of spine length (ii) enable calculation of spine motility (average change in length over time) or dynamics (iii). **(c)** The molecular cascade linking deprivation of visual input to structural changes in connections serving the deprived and non-deprived eyes. Postsynaptic Ca^{2+} signaling resulting from different patterns of activity following deprivation activates intracellular cascades, which lead to remodeling of the synaptic actin cytoskeleton, to changes in the extracellular matrix and to synthesis of proteins that support changes in function. This leads to the destabilization of spine structure, whereby spines receiving inputs from the deprived eye become more motile and are eventually lost. The axonal arbor is reorganized on a slower timescale.

[18]. This enables synapse-specific and input-specific functional specialization and plasticity. Additionally, spine morphology is highly plastic, and spine sizes increase and structural dynamics decrease as development proceeds [19–21]. Indeed, recent studies suggest that many aspects of spine structure can influence synapse function and that spine morphology, in turn, can be regulated by synaptic activity [22–25]. Rapid spine-head expansion occurs following stimuli that elicit long-term potentiation (LTP) in the hippocampus [26–28], and is more prominent and persistent at thin spines, which contain weaker synapses [29] and are more likely to undergo long-lasting potentiation [26]. Plasticity-dependent changes in spine size are bidirectional such that spines become smaller when their synapse undergoes depression [27,30]. Persistent spine expansion might be a developmental phenomenon, because the adult cortex displays a larger proportion of large mushroom spines, and a smaller proportion of thin spines, than developing cortex. Interestingly, experiments carried out in adult tissue show only a temporary expansion of spine heads following LTP [28].

Although the degree of spine remodeling in the adult cortex is still somewhat controversial [31,32], chronic imaging studies carried out *in vivo* suggest that spines turn over during development and become more stable in adult animals [31–35]. Spine turnover *in vivo* might be important for circuit remodeling by activity, based on electron-microscopic studies that link spine turnover to synapse formation and elimination [31]. *In vitro*, potentiating stimuli elicit spine and filopodial outgrowth during development [36,37] whereas depressing stimuli elicit spine loss [30,38]. Additionally, thin spines are more transient than mushroom spines [33], suggesting that they carry immature synapses with potential either to be potentiated and stabilized or to be eliminated. By comparison, axon terminals are less motile than dendritic spines [39] and are more persistent than dendritic spines *in vivo* [35]. Changes in spine-head shape can be rapid, and such changes might enable interactions with multiple stable presynaptic terminals [40].

Altering sensory activity elicits rapid changes in post-synaptic structure

Dendritic spine structure and persistence can also be regulated by sensory activity. In the visual system, prolonged binocular deprivation via either closure of both eyelids [41] or dark rearing [42] upregulates spine motility, consistent with the effects of synaptic activity *in vitro*. In the somatosensory system, however, whisker deprivation during an early postnatal period leads to reduction in spine dynamics [21], suggesting that spine morphology might be differentially regulated in the two sensory cortices. It is also possible that activity has different effects on spine dynamics in somatosensory and visual cortex at different ages. In older animals, whisker deprivation leads to an increased turnover of spines [31]. Paradoxically, a recent study found that whisker deprivation appears to reduce developmental spine loss, possibly in a homeostatic capacity [43]. This is at odds with studies carried out in the visual cortex, where dark rearing from birth reduces spine density [44]. Some of these differences might be due to different time courses of deprivation, and/or possible differences in sensitive periods for structural and functional remodeling in visual versus somatosensory cortex.

Although structural changes are classically thought to be secondary to, and proceed more slowly than, functional changes, recent experiments in visual cortex suggest that changes in structure can be rapid and accompany or even underlie the functional changes. For instance, two days of artificially induced strabismus, which alters the pattern of activity from the two eyes without altering the overall amount of activity, are sufficient to alter binocular horizontal connectivity [45]. At the synaptic level, dendritic spines undergo rapid morphological changes following deprivation (Figure 1c), and two days of monocular deprivation are sufficient to enhance dendritic spine motility [46].

However, axons are likely to remodel at a slower pace. Following monocular deprivation, thalamocortical axons from the non-deprived eye expand while those from the deprived eye shrink [47], although such changes require days or weeks to become apparent. The density of both excitatory and inhibitory presynaptic terminals also remains stable for a week following monocular deprivation [48]. This suggests that the dendritic spine provides the major basis for rapid structural plasticity, whereas the axon terminal network remains stable. The stability of axon terminals might enable rapid and precise recovery of responses following eye reopening [15,16,49,50], by acting as a scaffold to which postsynaptic neurons can reconnect. After the remodeling of axon terminals following a longer period of deprivation (Figure 1c), recovery might require prolonged stimulation and *de novo* protein synthesis for normal connectivity to be re-established. The timing of axon withdrawal might account for the recent report that physiological loss and recovery of eye-specific responses are independent of protein synthesis after short-term deprivation [15].

Activity-dependent changes involve specific synapses and pathways

The aforementioned studies indicate that monocular-deprivation-induced changes in response properties and in neuronal structure involve specific connections and sites of contact. Deprivation-induced changes in response properties are dramatic and rapid during the critical period, with a smaller effect observed before or after this time. However, recent experiments have shown that monocular deprivation can also cause changes in response properties of adult cortical neurons [51] and that prior experience of deprivation enhances this effect [52]. Response changes also occur in the adult visual cortex after focal removal or reduction of retinal activity. A restricted retinal lesion causes neurons in the denervated region of visual cortex to change their receptive-field location and size [53,54], mainly owing to an enhancement in the strength and subsequent growth of horizontal intracortical connections [55]. Remarkably, under-stimulation of a local region of retina combined with stimulation of a surrounding region also causes receptive fields in

the 'artificial scotoma' within visual cortex to expand considerably, within minutes [56].

Common to the findings on rapid receptive-field and ocular-dominance plasticity in the developing and adult visual cortex is the explanation that such plasticity involves a reduction in drive of one set of connections coupled with an enhancement in the strength of another set of connections to the same neurons. Thus, monocular deprivation reduces feedforward drive to neurons in deprived-eye domains; this reduction is balanced by an enhancement of lateral drive from neurons that receive input from the non-deprived eye, causing a change in neuronal ocular dominance. A central hypothesis underlying this proposal is that neurons seek to preserve a certain level of total drive, and thus compensate for a reduction in one set of inputs by increasing the strength of another. Recent findings on homeostatic regulation of synaptic strength by developing neurons [57] and on the requirement of neurons to balance their levels of excitation and inhibition [58,59] lend support to this hypothesis. Interestingly, the hypothesis predicts that specific molecular mechanisms, active during early development, regulate the set-point for a neuron and hence its propensity for plasticity.

Changes in cortical responses might then be rapid and pronounced in locations where neurons receive multiple sets of inputs. Indeed, rapid changes in response properties occur first in extragranular (and infragranular) layers, which receive both feedforward inputs and horizontal inputs, before spreading to layer 4 [14]. Changes in dendritic spine dynamics following short-term deprivation occur on the proximal dendrites (located in layer 5) and distal dendrites (located in layers 1 and 2) of layer 5 pyramidal neurons [46], but not on basal dendrites of layer 3 neurons (which spread into layer 4 and receive input directly from the thalamus) [60]. Laminar changes in response properties, connectivity and dendritic spine dynamics might additionally be tied to varying susceptibilities of connections in different layers to undergoing potentiation and depression [61].

Mechanisms of plasticity in the developing cortex

Recent research has shed light on the mechanisms responsible for translating electrical activity in afferents into functional and structural changes at synapses, which in turn are crucial for the remodeling of cortical networks and altered cortical function. Actin is the structural scaffold of the postsynaptic membrane [62] and is crucial for synaptic transmission and plasticity [63]. Not surprisingly, it also has a role in structural changes in spines during plasticity [64]. Synaptic potentiation leads to actin polymerization in the spine head, increasing spine size, whereas depotentiation leads to actin depolymerization, decreasing spine size [27]. The signaling pathways that link synaptic activity to changes in actin dynamics and altered synaptic structure and function are central for creating specific processing networks from a broad scaffold (Figure 1c).

One of the first signaling steps during synaptic activity is the influx of Ca^{2+} into the dendritic spine through postsynaptic NMDA receptors. Postsynaptic Ca^{2+} levels are thought to determine bidirectional synaptic plasticity [65]. NMDA-receptor-dependent changes in synaptic strength, especially synaptic depression, are thought to mediate changes in ocular dominance [66], and NMDA receptor function is crucial for ocular-dominance plasticity [67]. Additionally, Ca^{2+} influx during synaptic and cellular activity affects dendritic spine motility and changes in synapse shape [25].

Ca^{2+} signaling affects many intracellular kinases and phosphatases that have a role in synaptic plasticity [68]. Interestingly, many of these are upregulated during the critical period for binocular plasticity [69]. Of particular interest, the activity of Ca^{2+}/calmodulin-dependent kinase II (CamKII) is crucial for ocular-dominance plasticity [70], for LTP [71,72] and for plasticity-driven changes in spine shape [26,27]. Because different molecular pathways often affect one another, it is likely that many other kinases and phosphatases are involved in ocular-dominance plasticity. In fact, both cAMP-dependent protein kinase (PKA) and extracellular signal-regulated kinase (ERK) have recently been shown to have a role in visual plasticity [67]. Kinase activity might eventually lead to alterations in the actin cytoskeleton through the action of the rho family of GTPases, lim-kinases and actin-associated proteins such as cofilin, cortactin, profilin, drebrin and the catenins [63,73]. Additionally, kinase activity during ocular-dominance plasticity can lead to activation of cAMP-response-element-binding protein (CREB) [74], which results in the synthesis of new proteins, a process necessary for both ocular-dominance plasticity [75] and long-term changes in synaptic strength [73].

Extracellular molecules (Figure 1c) also influence ocular-dominance plasticity [76]. The dissolution of extracellular chondroitin sulfate proteoglycans (CSPGs) enables ocular-dominance plasticity to occur in adult animals, suggesting that the extracellular matrix matures to become non-permissive for plasticity following the close of the critical period [77]. Additionally, tissue plasminogen activator (tPA), which degrades the extracellular matrix, is also involved in ocular-dominance plasticity [78]. Interestingly, tPA regulates spine motility [46] and spine loss [79] and might act in a lamina-specific manner to enable structural synaptic plasticity to occur following brief monocular deprivation [46].

Rewiring cortex

Visual deprivation paradigms induce loss of function from the deprived eye (although following monocular deprivation, the non-deprived eye gains functional connections) and demonstrate that visual experience is permissive for making appropriate cortical connections. Experiments that rely on a gain-of-function approach offer complementary insights into the role of activity in shaping cortical networks, by demonstrating that visual experience is instructive for making specific connections. Thus, rearing kittens in an environment of one stimulus orientation leads to an over-representation of that orientation in visual cortex [80]. A unique way to probe the instructive effects of visual experience utilizes the routing of visual inputs to the auditory pathway. Removal

of inputs to the auditory thalamus induces the growth of retinal axons into the auditory thalamus, providing visual drive to the auditory pathway [7] (Figure 2a). In animals where visual input is 'rewired' in this way, auditory cortex shows many of the structural characteristics of visual cortex. For instance, rewired ferret auditory cortex responds to visual stimulation, and neurons in the rewired cortex exhibit properties such as orientation and direction selectivity. Interestingly, in these animals, cells responding to similar orientations are grouped into an orientation map, and intracortical long-range connections (Figure 2b) acquire a patchy distribution similar to that found in visual cortex [81]. Additionally, this new connectivity can drive visual behavior from the auditory cortex [82] and induce learning such as fear conditioning via projections to the amygdala and subsequent pathways [83] (Figure 2a).

Generation of orientation selectivity in rewired auditory cortex provides a dramatic example of the role of visual activity in shaping intracortical connections and networks. Various experimental and computational studies support the view that orientation selectivity in a visual cortical neuron derives from feedforward inputs from the visual thalamus that are aligned along the axis of orientation, coupled with local recurrent excitatory connections that amplify these inputs and inhibitory connections that dynamically stabilize the excitation [59,84]. We propose that the generation of orientation selectivity in rewired auditory cortex follows a similar principle, with inputs from the retina via the auditory thalamus reflecting the correlated local orientation structure of the visual world [85] and recurrent connections in the cortex being crucial in sharpening selectivity (Figure 2c). The long-range connections of both visual cortex and rewired auditory cortex (Figure 2b) would similarly derive from the nature of correlations in the visual world acting in concert with activity-dependent mechanisms and molecules present in the cortex.

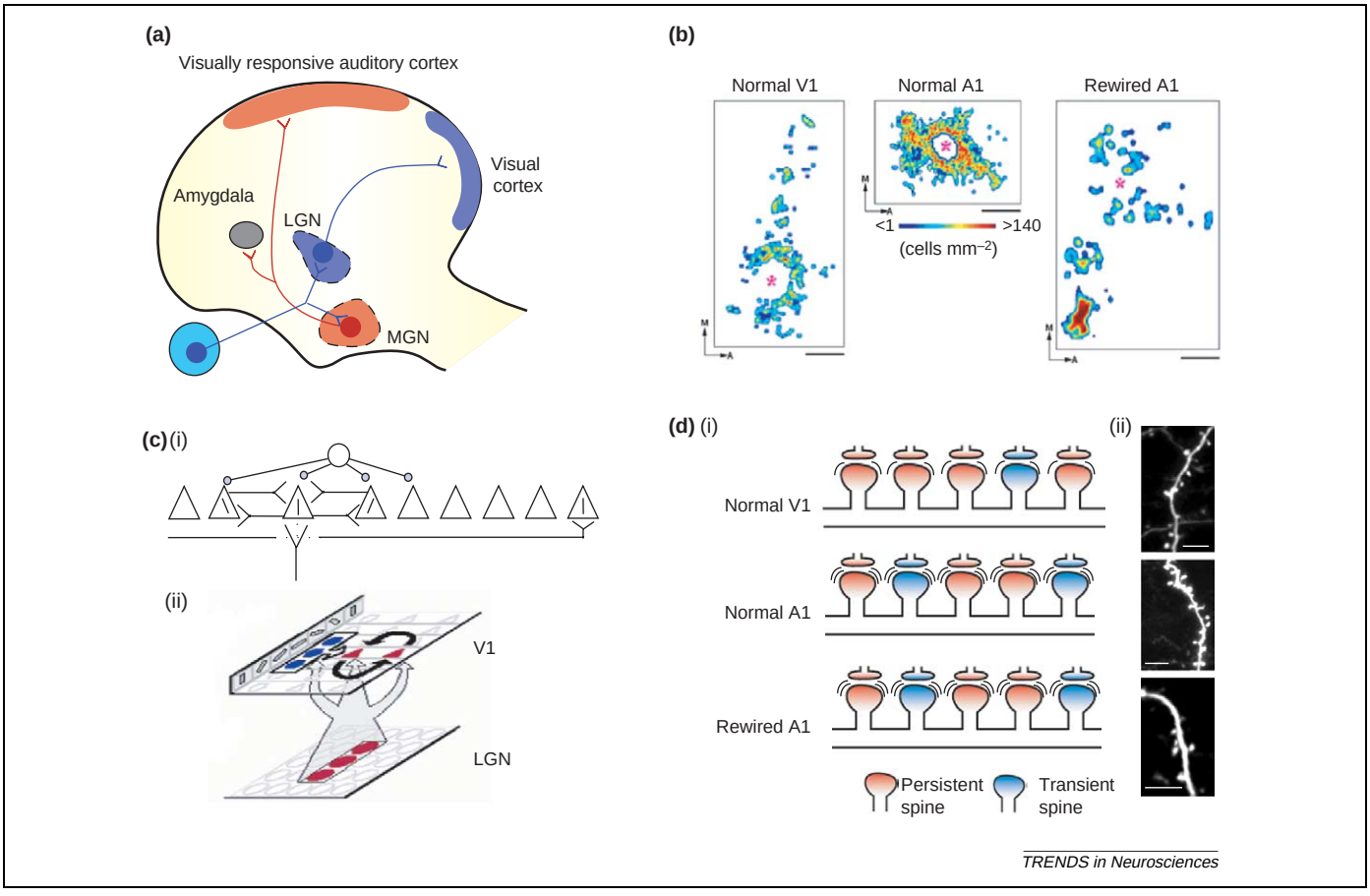

Figure 2. Rewiring visual input to the auditory pathway as a model for studying activity-dependent plasticity in the cortex. **(a)** Retinal axons can be induced to innervate the medial geniculate nucleus (MGN), effectively enabling visual inputs to drive the auditory cortex. This is achieved by lesioning the inferior colliculus, which normally projects to the MGN, in neonatal ferrets. Visual pathways are shown in blue and normal auditory pathways are shown in red. **(b)** Rewiring visual input into the auditory cortex induces restructuring of connections in auditory cortex. Long-range connections in primary visual cortex are patchy and link cells with similar orientation preference. In the primary auditory cortex, long-range projections are oriented along the isofrequency axis of the cortex. However, in rewired auditory cortex, these projections are patchy and resemble projections in primary visual cortex. In the experiments shown here, intracortical connections were labeled by injecting cholera toxin B into the cortical sites marked by pink asterisks. Adapted, with permission, from Ref. [81]. **(c)** In the primary visual cortex (V1), orientation-biased feedforward connections from the LGN are amplified by local recurrent connections between excitatory neurons (red triangles) to generate sharp orientation tuning (ii). Inhibition (blue) is nonspecific for orientation but balances excitation to preserve tuning. Sharp orientation tuning in rewired auditory cortex might be set up in a similar manner, with feedforward connections from the thalamus setting up rough orientation tuning and local connections then refining and sharpening selectivity. Adapted, with permission, from Ref. [84]. (i) Long-range connections link excitatory neurons (triangles) that have similar orientation preference, in both primary visual cortex and rewired auditory cortex (b), whereas inhibitory neurons (circles) provide nonspecific inhibition that balances excitation. **(d)** On a synaptic level, rewiring visual input into the auditory pathway does not alter the structural stability of dendritic spines in terms of spine motility and persistence. Morphology of dendritic spines in V1, A1 and rewired A1, illustrated schematically (i) and assayed by *in vivo* two-photon microscopy (ii). Spine dynamics are similar in A1 and rewired A1, and greater than in V1. Thus, the dynamics of dendritic spines are probably determined by cues intrinsic to the cortical area. Scale bars, 5 μm.

Although these experiments show that activity can remodel cortical networks, it is clear that activity is not the only determinant of cortical structure. Rewired auditory cortex takes on many properties of visual cortex but also retains some of its original network properties. Rewiring appears not to alter the structure of thalamocortical arbors, and intracortical connections, though patchy, are not as regular and precise as those in visual cortex. Orientation maps in rewired auditory cortex show less periodicity and larger orientation domains than those in visual cortex [81]. Additionally, on a synaptic level, spine dynamics in rewired auditory cortex are more similar to those observed in normal auditory cortex than to those of visual cortex, where spines are more stable [35] (Figure 2d). These findings argue that although activity has a powerful ability to remodel cortical connections, it probably acts in concert with a scaffold of connectivity laid down by intrinsic cues.

Future directions

Cortical networks are the engine of the brain, for they transform simple inputs into complex outputs that mediate brain functions and behavior. High-resolution methods of visualizing single synapses and even single molecules within synapses are transforming our understanding of the mechanisms that create cortical connections. Important insights into the plasticity of network properties will be gained from imaging neuronal function on a single-cell level while monitoring network activity. Recent advances in imaging Ca^{2+} *in vivo* using extrinsic dyes [86] or genetic reporters [87], and the future development of sensitive voltage reporters [88], make this an attractive avenue of research. Functional imaging of single-cell activity *in vivo* combined with molecular markers that might provide information as to cellular identity will enable the determination of network connectivity and its plasticity following activity-dependent manipulation. Furthermore, the imaging of molecular changes in single cells and even synapses will provide more insight into the mechanisms governing fast structural changes that result in rapid functional plasticity. Importantly, it will enable the examination of specific hypotheses regarding mechanisms of plasticity, such as those involving the rapid replacement of one set of functional inputs by another and the molecular set-points that govern such changes.

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