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The development of local circuits in the neocortex: recent lessons from the mouse visual cortex

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Abstract

Precise synaptic connections among neurons in the neocortex generate the circuits that underlie a broad repertoire of cortical functions including perception, learning and memory, and complex problem solving. The specific patterns and properties of these synaptic connections are fundamental to the computations cortical neurons perform. How such specificity arises in cortical circuits has remained elusive. Here, we first consider the cell-type, subcellular and synaptic specificity required for generating mature patterns of cortical connectivity and responses. Next, we focus on recent progress in understanding how the synaptic connections among excitatory cortical projection neurons are established during development using the primary visual cortex of the mouse as a model.

Introduction

The neocortex is composed of many different types of neurons, each with distinct patterns of synaptic connectivity conferring different functions *in vivo*. The majority of these cell types are excitatory cortical projection neurons, with intracortical axons forming local synaptic connections within the cortex and long-range axons targeting distinct subsets of distant cortical and subcortical regions [1–3]. Although precise patterns of local intracortical synaptic connections are essential for proper cortical function, how local cortical circuits are established remains elusive. With the advent of two-photon *in vivo* imaging combined with whole-cell recordings of unitary synaptic connections among other techniques, recent work focused on mouse primary visual cortex (V1) has begun to shed light on the time course and mechanisms that generate the mature patterns of intracortical synaptic connections and resulting response properties of cortical neurons.

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Conflict of interest statement

Nothing declared.

Mouse visual cortex as a model for cortical circuit development

The primary visual cortex of the mouse is traditionally divided into six layers. Following the canonical cortical microcircuit, incoming sensory information primarily enters layer 4 (L4), passes to layer 2/3 (L2/3) and then on to layers 5 and 6 (L5, L6) [4–6]. Although early work suggested that neurons with different response properties in mouse V1 were intermingled in a 'salt-and-pepper' pattern [7–9], recent studies have demonstrated more functional organization than previously appreciated [10,11••,12•,13•,14]. For instance, neurons that share orientation preferences are weakly clustered into vertical columns [12•,13•], and L5 pyramids with similar long-range projection patterns are also clustered into micro-columns in mouse V1 [10,11••]. In the horizontal plane, clusters of L2/3 neurons with distinct tuning preferences are aligned with patches of M2 muscarinic acetylcholine receptor expression and L1 patches, defined by the termination patterns of geniculocortical and feedback inputs into V1 [14]. Taken together, these studies indicate that the patterns of synaptic connectivity in mouse V1 exist within a columnar and tangential cortical organization.

Specificity of synaptic connections within the neocortex

Within this overarching organization, cortical projection neurons form precise synaptic connections defined at different scales. First, they establish cell-type specific patterns of synaptic connections. For example, the probability of forming synaptic connections among different classes of L5 cortical projection neurons defined by their long-range axonal targets depends on the identity of the presynaptic and postsynaptic cell types [15–17]. Similarly, L2/3 neurons defined by similar receptive field properties are preferentially connected [18,19•,20,21•]. Second, specific subcellular compartments of projection neurons receive distinct synaptic inputs. Inhibitory Chandelier cells, which synapse onto the axon initial segments of cortical projection neurons, are perhaps the most famous example [22]. However, Chandelier cells are not exceptional as other classes of inhibitory neuron similarly target particular dendritic compartments of cortical projection neurons [23,24]. Similarly, long-range inputs to the cortex also synapse onto specific dendritic compartments [25] as do local connections among cortical projection neurons [26–31]. Third, alongside specificity in target choice and location for synapse formation, developmental mechanisms must establish the appropriate synaptic properties for each connection (for review, see [32]). For example, in addition to being preferentially interconnected, L2/3 neurons with shared response properties also form stronger synaptic connections than average [19•,21•]. These studies highlight the many challenges in establishing the mature patterns of intra-cortical synaptic connectivity that shape the activity of adult cortex.

Clonally related neurons are connected via gap junctions in the first postnatal week

One possibility is that cell lineage seeds the initial synaptic organization of local cortical circuits. Radial glial progenitors (RGPs) in the ventricular zone generate cortical neurons in an inside-out fashion, such that L6 neurons are born first and L2 neurons last. This process produces clonally related sister neurons arising from the same RGP that may represent the basis of the cortical column [33]. Gap junctions, which mediate coordinated electrical

activity and the passage of small molecules among connected cells (for review, see [34]), preferentially connect vertically aligned, clonally related neurons through the first postnatal week before disappearing by postnatal day (P)6 [35,36••] (Figure 1, *P0–P6 panel*). These clonally related sister neurons go on to preferentially form chemical synaptic connections after the initial electrical connections have been eliminated [35,37]. Strikingly, these chemical connections within ontogenetic columns reflect the flow of information through the canonical cortical microcircuit, from L4 to L2/3 to L5 and L6 [37]. The formation of these early gap junctions and the subsequent preferential chemical synaptic connections among sister neurons is disrupted when normal neuronal migration is disturbed either by abolishing Reelin signaling, essential for the normal inside-out development of the neocortex, or by altering the tangential migration of sister neurons through Ephrin-A signaling [36••].

Projection neurons within cortical microcolumns are connected via gap junctions

In addition to clonal networks, small clusters of vertically aligned neuronal cell bodies form microcolumns within the cortex [10,11••,12•]. The neurons within microcolumns share long-range axonal projection patterns [10], and these cell-type specific columnar clusters in L5 tile the cortex in a hexagonal lattice, with a period of approximately 30 μm [10,11••]. Although most neurons in a microcolumn are not clonally related, they are also electrically coupled early in cortical development via cell-type specific gap junctions [11••] (Figure 1, *P7–P14 panel*). Unlike gap junctions among clonally related sister cells which have largely disappeared by P6–7 [35], the electrical coupling within L5 microcolumns persists longer, becoming undetectable around P10–14, before the time of eye opening [11••]. In contrast to clonally related cortical neurons, no preferential chemical synapses were found within microcolumns after gap junctions among neurons within a microcolumn had disappeared [11••,38]. However, neurons within microcolumns share strong, common synaptic inputs [11••]. The relationship between electrical coupling of clonally related neurons and electrical coupling of neurons within microcolumns remains unclear.

Inhibiting gap junctions in early development disrupts cortical circuit formation

These early electrical connections play an important role in establishing local cortical connections and cortical receptive field properties [35,39,40]. Connexin26 is a gap junction protein highly expressed in the developing cortex. Expressing a dominant negative form of Connexin26, for example, in L2/3 projection neurons starting at embryonic day (E) 12–13 reduced the subsequent formation of preferential chemical synaptic connections between related sister neurons in V1 of P12–17 mice [35] and also the similarity in response properties among sister neurons [40]. However, any differences in the contributions of gap junctions specifically among clonally related neurons, among neurons within a microcolumn, or among yet to be defined neurons to the initial establishment of cortical circuits, remains to be clarified.

How these gap junctions influence the later synaptic organization of cortical circuits also remains unclear. One possibility is that spontaneous activity before eye opening coordinates the activity of electrically coupled neurons [35] and contributes to the initial formation of preferential connectivity between neurons that share receptive field properties [18,19•, 20,21•,41]. Modeling studies suggested that cell pairs are more likely to stabilize the same set of feedforward thalamocortical inputs and share similar receptive field properties if they were connected via gap junctions during the first postnatal week [41]. This prediction is consistent with the finding that clonally related sister neurons have more similar orientation preferences than unrelated cortical neurons in mature circuits [40,42].

Contributions of neural activity to early circuit formation

Early in development, the transmission frequency of dendritic spine responses that are poorly synchronized with their neighbors during spontaneous activity becomes reduced [43]. This process may contribute to functional clustering of spines within the dendritic arbor of cortical neurons [44•,45] and the formation of strong, shared, inputs between L5 neurons within a microcolumn [11••]. The resulting clustering of coordinately active inputs may also be reflected in the clustered distribution of synaptic inputs with particular receptive field properties within the dendritic arbors of mature L2/3 neurons: spines responding to the same location in visual space as a neuron's receptive field preferentially cluster on neighboring spines of proximal dendrites while spines responding to regions beyond the receptive field are found on higher order branches [44•].

These findings have been interpreted to mean that mechanisms dependent on spontaneous activity prior to eye opening underlie the formation of early cortical circuits. However overexpression of the potassium channel Kir2.1, to suppress L2/3 neurons beginning at late embryonic stages, suppressed spontaneous activity before eye opening but did not affect the initial development of orientation and direction selectivity, suggesting that these receptive field properties develop in an activity-independent manner [46••]. Whether this manipulation affected the pattern of chemical synaptic connections among neurons with similar receptive field properties or among clonally related neurons akin to inhibition of gap junctions was not tested. Thus, the precise mechanisms by which gap junctions and spontaneous activity contribute to the patterns of synaptic connectivity in mouse V1 prior to visual experience remain to be fully elucidated.

Molecular contributions to early cortical development

Additional molecular mechanisms have also been implicated in establishing synaptic relationships prior to visual experience, but how they influence specificity in circuit formation is not well understood. For example, a recent study implicated Dnmt3b DNA methyltransferase in stabilizing reciprocal chemical connections among clonally related layer 4 sister neurons in somatosensory cortex [47]. The authors proposed that methylation patterns influence the expression patterns of clustered protocadherins, cell adhesion molecules thought to play roles in self-recognition and non-self-recognition [47]. Other molecular mechanisms involved in input-specific regulation of synapse formation in primary somatosensory cortex may also contribute to circuit formation in V1 [43,48], as may

mechanisms implicated in the regulation of synapse formation in specific cortical cell types and dendritic compartments [49–52]. Together, these studies demonstrate that, before visual experience, multiple mechanisms likely work in concert to establish early patterns of synaptic connections that generate initial receptive field properties — including the spatial structure, orientation tuning, and direction preference of mouse V1 neurons [41,46••,53–55].

Changes in synaptic connectivity following eye opening in the mouse

Significant synaptogenesis and maturation of receptive field properties occurs around eye opening (around P14), but little is known regarding the specific changes in cortical circuits during this time period [56,57]. The patterns of synaptic connectivity and selectivity in receptive field properties continue to be shaped after eye opening (Figure 1, *P14–P21 and P22+ panels*). However, only some of these changes depend on visual experience. For example, prior to eye opening, the preferential connectivity between L2/3 neurons with similar orientation preferences is immature. Only after eye opening does the probability of synaptic connection among L2/3 pyramids with similar receptive field properties and the proportion of bidirectionally connected L2/3 neurons sharing receptive field properties increase significantly, as does the synaptic strength of these connections [19•,41,58,59••]. This increase in preferential connectivity represents both an increase and strengthening of connections among L2/3 neurons with similar response properties as well as a decrease in the connectivity of non-responsive neurons [41,59••]. Interestingly, the emergence of reciprocal synaptic connections among neurons with shared response properties proceeds largely unaffected by the absence of visual experience [59••]. In contrast, the elimination of connections among visually non-responsive L2/3 neurons was inhibited by dark-rearing [59••]. The significant increases in the probability of connection and synaptic strength among randomly selected L2/3 neurons in rats following eye opening were also eliminated by dark-rearing but not by binocular eyelid suturing [58], suggesting a role for patterned visual input. Whether visual experience shapes the chemical connections formed among clonally related sister neurons has not been tested.

As with the patterns of intracortical connectivity, only some changes in receptive field properties following eye opening are dependent on visual experience. For example, the correspondence between ON and OFF subfields received from the two eyes and binocular matching of orientation preferences in mouse V1 is disrupted by dark-rearing, although experience-independent mechanisms generate the ON and OFF subregions and the overlap of the receptive fields in visual space [54,55]. The broadening of the orientation tuning of L2/3 fast-spiking neurons was also disrupted by dark-rearing [60]. In contrast, the elimination of initial biases in the distribution of preferred orientations and preferred directions in L2/3 excitatory neurons required neuronal activity but not visual experience [46••,53,60]. The sparsification of V1 neuronal responses in L2/3 also proceeded, although delayed, without visual experience [61]. How the evolution of response properties during the first weeks following eye opening relates to underlying changes in synaptic connectivity remains unclear. Furthermore, the contributions of molecular mechanisms implicated in shaping synaptic connections in visual and somatosensory cortex in later development, including specifying connections among cortical neurons at the cell-type or subcellular levels, remains to be fully elucidated [48,50,62,63••,64] (for reviews, see [65,66]).

Nonetheless, together, these results indicate that experience-dependent, activity-dependent and activity-independent mechanisms contribute to cortical circuit development after eye opening.

Summary

The advent of two-photon imaging of calcium indicators in combination with recordings of unitary synaptic connections has begun to generate insights into how the patterns of synaptic connectivity in primary visual cortex of the mouse change during development. However, technical limits of these approaches have largely limited analyses to the supragranular layers of the cortex and to only a subset of time points and conditions. Many studies focus only on one level of specificity, making it challenging to understand how mechanisms may work in concert. Do, for example, molecular signals guide axons to a particular cortical layer to restrict the choice of available targets for synapse formation while additional mechanisms confer further cell-type or subcellular specificity? Whether all synaptic connections require each of these levels of specificity also remains unclear. For example, a recent study suggested that L4 spiny stellate cells target the apical tufts of L6 pyramids, while L4 star pyramids target basal and proximal dendrites, exhibiting compartment-specific targeting [31]. However, these connections did not distinguish between the type of L6 neurons targeted, L6 corticothalamic neurons or L6 corticocortical neurons, thus showing no specificity with regard to cell type. Generating a framework that integrates these distinct levels of specificity, and understanding how different mechanisms, including experience-dependent, activity-dependent and activity-independent processes, work in concert to produce mature cortical circuits remain important challenges.

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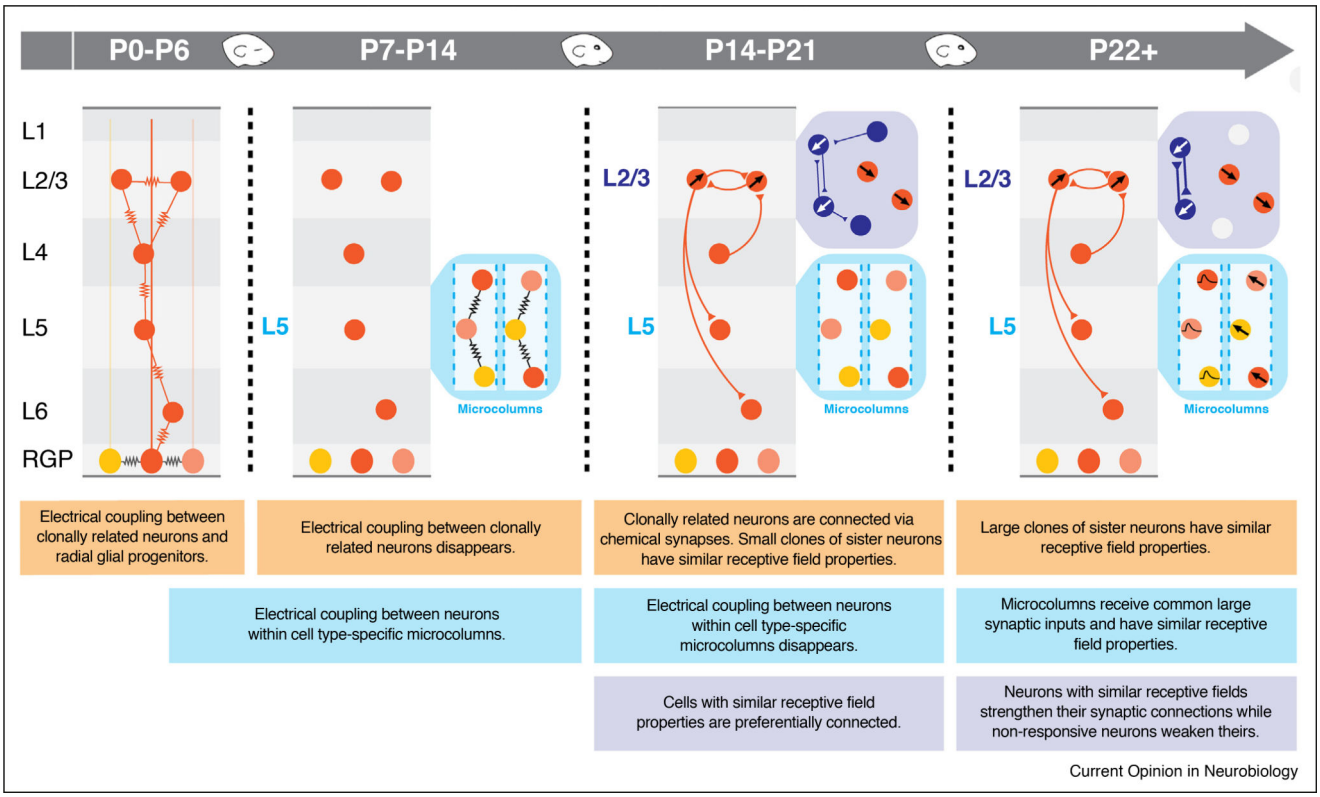

Figure 1.

Development of intracortical synaptic connections in the visual cortex of the mouse. The formation of specific patterns of intracortical synaptic connectivity is regulated by activity-dependent and independent mechanisms. Because most studies sample only a subset of developmental time points, the precise biological start and end of the processes illustrated and their temporal relationships remain unclear. How these mechanisms act together to elaborate synaptic connections among clonally related cortical projection neurons (orange), among neurons in cortical microcolumns (cyan), and among neurons with related response properties (dark blue) at the cell-type, subcellular and synaptic level remains to be fully elucidated.