Chapter 7

Circuit development in somatosensory cortex

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7.1 Introduction

Primary somatosensory cortex is the region of neocortex specialized to represent and process touch, which includes light touch and proprioception, as well as temperature and pain. In primates, primary somatosensory cortex is found posterior to the central sulcus, posteriorly adjacent to primary motor areas. In humans, it includes four Brodmann areas (from the central sulcus moving posteriorly): areas 3a, 3b, 1, and 2 (Brodmann, 1909). Each area contains a distinct somatotopic body representation (Penfield and Jasper, 1954). The areas differ in the type of information (proprioception vs. touch) represented. Following Vernon Mountcastle's first description of the columnar organization of neocortex (Mountcastle, 1997), somatosensory cortex became fundamental to our understanding of cortical circuitry. The basis of columnar organization is that neurons in the same column show similar functional properties across cortical depth, whereas adjacent columns have different functional properties.

Somatosensory and visual cortices have been the primary models for understanding the connectivity and function of local neocortical circuits for decades. Both are prominent in primates and other placental mammals including rodents. Both contain six cortical layers with characteristic local and long-range projection patterns from the excitatory cells in each layer. The cortical layers are numbered L1 to L6 (L1 for layer 1, for example). Sublaminae are noted by letter, such as L5A and L5B. With the advent of transgenic tools to target and manipulate specific cell types, rodent models have become of increasing importance in identifying the range of cell types and unraveling their connectivity, although the complexity of rodent sublamination may not be as extensive as that of primates. Due to the ease with which both somatosensory and visual inputs can be manipulated, both systems have also been used extensively to characterize normal developmental events and also to intervene in the normal developmental trajectory to determine the role of molecular cues and neural activity—including both spontaneous activity and patterned sensory input—in developing cortical circuitry.

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A large area of rodent primary somatosensory cortex, termed barrel cortex, derives its name from distinct anatomical structures in layer 4 that resemble the shape of a whiskey barrel. Within the granular layer 4, each barrel consists of a ring of densely packed cells surrounding a barrel hollow with reduced cell density (Woolsey and Van der Loos, 1970). Barrel cortex receives sensory input from the large facial whiskers. Throughout the ascending pathway (Figs. 7.1 and 7.2), the topographic representation of the whiskers is preserved, projecting to an ordered array of barrelettes in the brain stem trigeminal nucleus, barreloids in thalamic ventroposteromedial (VPM) nucleus, and barrels in primary somatosensory cortex (Haidarliu et al., 2008; Land et al., 1995; Van Der Loos, 1976). In cortex, each barrel is separated tangentially from its neighbors by a narrow area called a septum (Woolsey and Van der Loos, 1970). These septa are larger and more amenable to study in rats than mice, and it is unclear if homologs exist in primate somatosensation.

Individual barrels represent single whiskers. Barrel cortex contains a topographic map of the large facial whiskers, as seen in tangential sections through layer 4 (Woolsey and Van der Loos, 1970). In mice and rats, whiskers are organized into rows A–E (from superior to inferior) and columns 1–4 (from posterior to anterior), with additional outlier whiskers α, β, γ, and δ (posterior to and interdigitated between rows A–E; Dorfl, 1982). Barrel cortex not only is prominent in rodents but can also be found in some species of insectivores and lagomorphs, as well as a few marsupials (Fox, 2008). The representation and relationship between whiskers and barrels has been a useful tool in dissecting the relationship between external sensation and the cortical representation of touch, as manipulations of sensory experience can be addressed at multiple levels, ranging from the functional response in vivo to the strength of connectivity ex vivo and the appearance of barrels in fixed tissue.

7.2 The mature cortical circuit

Understanding of the local and long-range circuitry of primary somatosensory areas has come about slowly due to the inherent challenges in dissecting any cortical circuit: Cortical areas contain large numbers of cells and cell types. Individual barrels of barrel cortex may contain ~6500 neurons (in the smaller mouse) or ~19,000 neurons (in the larger rat), of

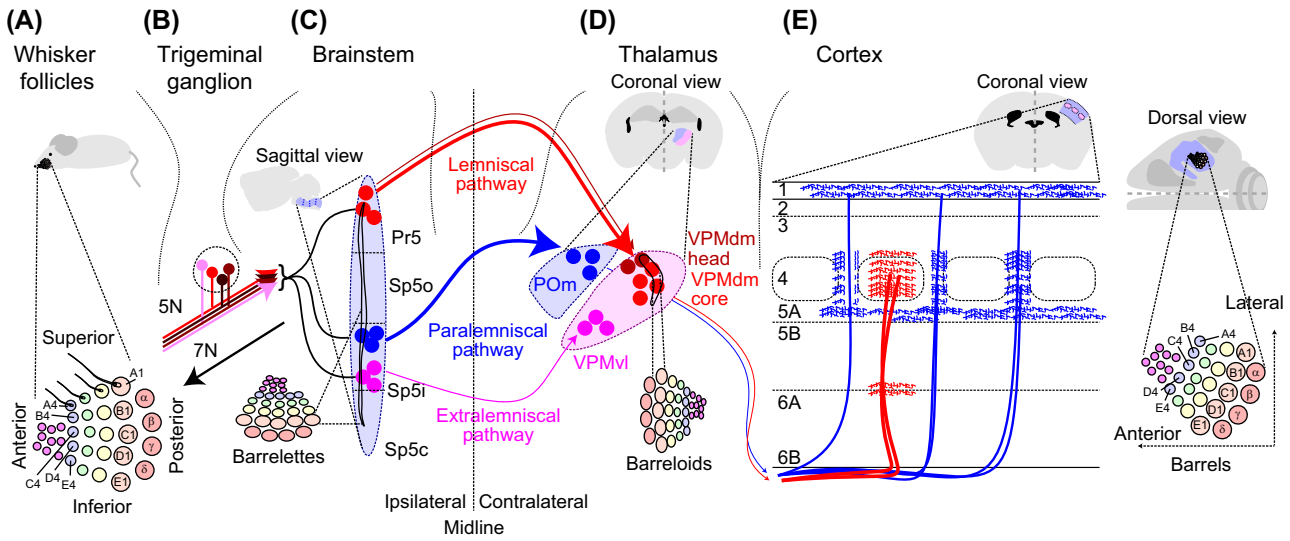

FIGURE 7.1 **Ascending pathways to somatosensory cortex.** (A) The whisker pad of the mouse, shown for the left side. Whisker rows (A–E) are numbered from posterior to anterior, with microvibrissae anterior. The color code is repeated through the figure to provide alignment. Four whiskers interdigitated between the posterior end of the rows are labeled with α, β, γ, and δ. (B) The somata of mechanoreceptors innervating the whisker follicle are in the trigeminal ganglion, entering the brain via the fifth cranial nerve (trigeminal). (C) Somatosensory input from mechanoreceptors enters the brain stem in the principal trigeminal (Pr5) and spinal trigeminal (Sp5) nuclei, which include oral (O), interpolar (I), and caudal (C) subdivisions. These nuclei contain topographically organized, elongated structures called barrelettes (the brain stem equivalent of the cortical barrels). Cells here are the origin of the ascending lemniscal (red, Pr5), paralemniscal (blue, Sp5i rostral), and extralemniscal (purple, Sp5i caudal) pathways to the thalamus. These pathways cross the midline, such that the whiskers and brain stem nuclei on the left are represented in the right thalamus and cortex. (D) Thalamus contains a principal thalamic nucleus, ventroposteromedial (VPM) that provides the main ascending input to primary somatosensory cortex (S1). The dorsomedial region of this nucleus contains topographically organized, elongated structures called barreloids (the thalamic equivalent of the cortical barrels), which have head and tail regions innervated by distinct segments of the lemniscal pathway and differ in functional properties. The dorsomedial core (VPMdm core) is the principal source of ascending input to cortical L4 in S1. Ascending VPM pathways are shown in red. The paralemniscal inputs target a higher order thalamic nucleus, the medial division of the posterior nucleus. Ascending posterior nucleus of thalamus (POm) pathways are shown in blue. (E) Cortical inputs from VPM (red) and POm (blue) differ in their laminar targeting and the extent to which they extend beyond the barrel corresponding to a principal whisker. The arrangement of the cortical barrels on the dorsal surface of cortex is shown for the right hemisphere, corresponding to the left whisker field.

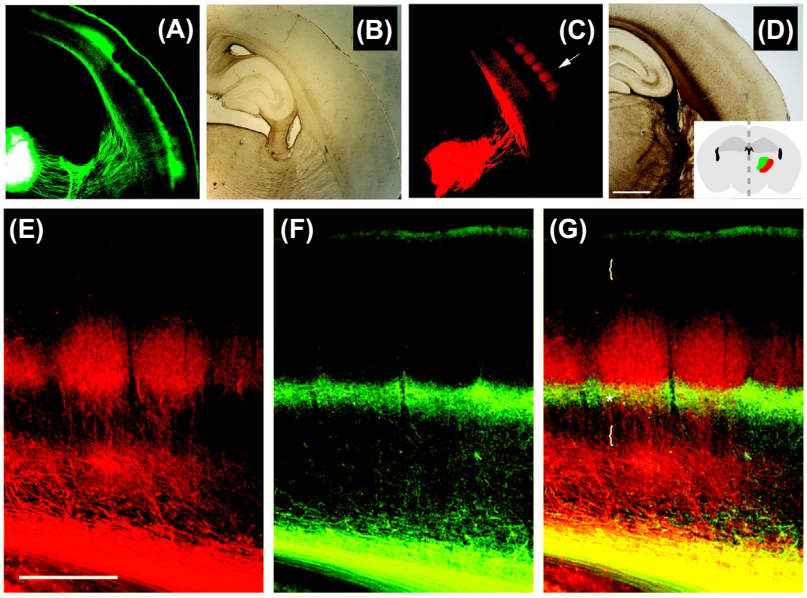

FIGURE 7.2 Fluorescence images of two ascending thalamocortical pathways to somatosensory cortex. (A, B) Bright-field and fluorescence images of coronal section of rat brain, showing POm axons expressing fluorescent proteins (green). (C, D) Bright-field and fluorescence images of coronal section of rat brain, showing VPM axons expressing fluorescent proteins (red). *Arrow* indicates a single barrel. Scale bar, 1 mm. (E–G) Dual label of thalamic axons. VPM (red) and POm (green). Zones with reduced afferentation marked with { in L2/3 and the upper portion of L5B. * indicates some overlap of VPM and POm in the deeper portion of L4. Scale bar, 0.5 mm. *POm*, posterior nucleus of thalamus; *VPM*, ventroposteromedial. *From Wimmer, V.C., Bruno, R.M., de Kock, C.P., Kuner, T., Sakmann, B., 2010b. Dimensions of a projection column and architecture of VPM and POm axons in rat vibrissal cortex. Cerebr. Cortex 20, 2265–2276.*

which ~10% are GABAergic interneurons (Feldmeyer, 2012; Feldmeyer et al., 2018; Lefort et al., 2009; Svoboda et al., 2010). Originally, advances in staining techniques led scientists to explore cell types in the neocortex. Nissl staining allowed clear visualization of large numbers of cells because of one basis for classification of the laminar organization of neocortex (Brodmann, 1909). Golgi staining enabled detailed visualization of the diversity of darkly labeled individual neurons residing in the cortex (Cajal, 1995). This diversity was apparent not only in the subtle differences in dendritic arborization between different pyramidal neurons but also in the tremendous diversity of local circuit interneurons. These differences in axon and dendrite morphology form one basis for the classification of cortical neurons into distinct cell types. In addition to structure, cell types may also differ in functional characteristics such as intrinsic excitability or receptive field pattern, or molecular traits, such as differences in gene expression that mark distinct interneurons and pyramidal cell types.

Thus, with the simplifying assumption that neural connectivity for typical neurons is roughly proportional to axodendritic overlap (Peters and Payne, 1993), anatomists began to explore local connectivity. For barrel cortex, this can be done by sampling large numbers of somatosensory cortical cell types and reconstructing the likely connectome (Egger et al., 2014). Anatomical approaches have been complemented with functional methods for measuring connectivity, including paired recordings (Lefort et al., 2009), laser scanning photostimulation (Callaway and Katz, 1993; Kotter et al., 1998; Shepherd et al., 2003), and channelrhodopsin-based optogenetic methods for circuit mapping (Petreanu et al., 2007, 2009). Genetically modified rabies approaches for mapping connectivity have also been developed (Wickersham et al., 2007). Functional assessments of connectivity have technical limitations, especially in slice recording where connections may be severed. But these functional approaches may be important in testing how specific cortical connectivity can be, identifying patterns between cell types where specificity exceeds that expected by axodendritic overlap (Shepherd et al., 2005). In sensory areas where similar excitatory cells in the same layer have diverse receptive fields (such as responding to stimuli moving in different directions), such functional assessments of connectivity are crucial to demonstrate that cortical connectivity can indeed be highly precise based on the response properties of identified cells (Bock et al., 2011; Ko et al., 2011).

7.2.1 Supragranular excitatory neurons

Based on axonal and dendritic morphology, for example, reconstructions suggest that there are at least 10 types of excitatory pyramidal neurons (Fig. 7.3) in rodent somatosensory cortex (Feldmeyer et al., 2013; Narayanan et al., 2015, 2017). While all excitatory neurons in the supragranular layers are pyramidal neurons (Binzegger et al., 2004), there are

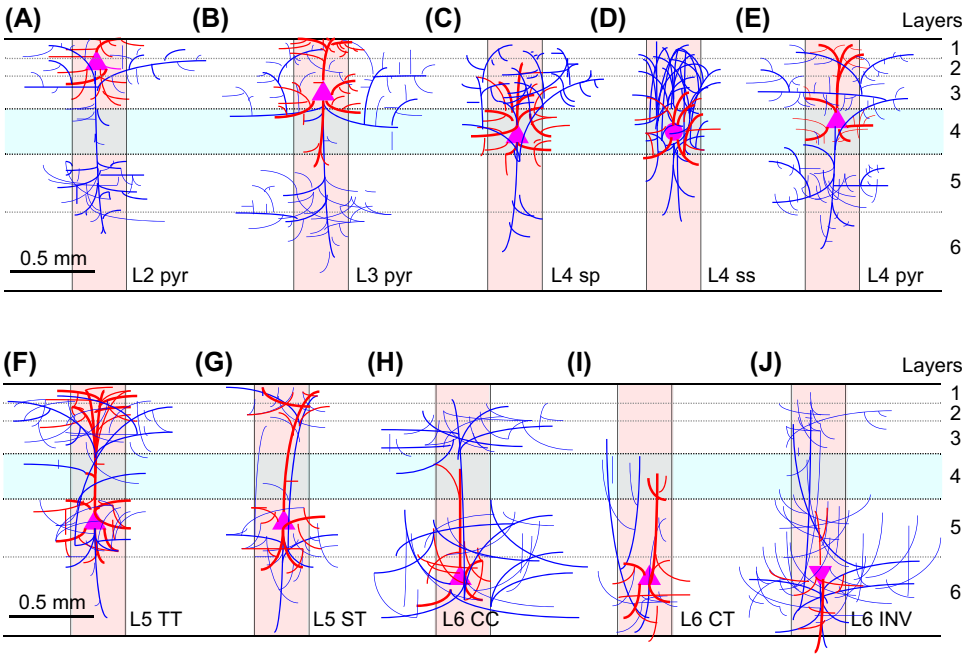

FIGURE 7.3 Principal excitatory cell types of somatosensory cortex. (A) Cartoon of axons (blue) and dendrites (red) of L2 pyramidal neuron in rat S1. Coronal view (along a whisker arc). Layers indicated by dashed lines and labeled at right. Blue layer indicates L4. Red column estimates the size of a barrel column. Scale bar 0.5 mm. (B-E) Similar presentation for a L3 pyramidal neuron (B), a L4 star pyramid (C), a L4 spiny stellate cell (D), and a L4 pyramid (E). (F-J) Similar presentation for a a L5 thick tufted pyramidal neuron (F), L5 slender tufted pyramidal neuron (G), a L6 corticocortical pyramidal neuron (H), a L6 corticothalamic pyramidal neuron (I), and a L6 inverted pyramidal neuron (J). *From Narayanan et al. (2015) Cerebral Cortex 25: 4450-4468.*

distinct L2 and L3 pyramidal cell types. Cell density makes it challenging to differentiate between L2 and L3 in rodents; thus, these layers are grouped by many investigators into a single layer, L2/3. L2 pyramidal cells occur in a relatively narrow region near L1 and thus have apical dendrites emerging from the cell body near L1. L2 pyramidal cells contrast with those in L3 in their local connectivity by receiving substantially reduced L4 excitatory innervation (Bureau et al., 2006; Hooks et al., 2011). L2 pyramidal cell dendrites and axons are more confined to the supragranular layers. L3 pyramidal cell axons are more likely to target L5. Both L2 and L3 pyramidal neurons send predominantly horizontal axonal projections inside and outside the principal barrel column that remain mostly supragranular (Narayanan et al., 2015). The descending excitatory projection from L2 to L5 targets mostly upper L5A cells, whereas L3 targets both L5A and L5B cells, resulting in a supragranular (L2/3) to infragranular (L5) connection pattern with superficial portions of L2/3 targeting superficial portions of L5. Correspondingly, deep portions of L2/3 target deep portions of L5. Since this projection pattern from L2/3 to L5 is present in multiple cortical areas, it is also one of the canonical intracortical pathways of neocortex (Hooks et al., 2011; Weiler et al., 2008).

In addition to intracortical projections, L2/3 pyramidal neurons send long-range projections to corticocortical targets, including primary motor cortex (M1) and secondary somatosensory cortex (S2). It has been suggested that these are two distinct populations of M1- or S2-projecting pyramidal cells (Chen et al., 2013, 2015; Sato and Svoboda, 2010). Some examples of cells projecting to both S2 and M1 cells exist in rat, however (Chakrabarti and Alloway, 2006). The degree to which L2/3 pyramidal neurons with distinct long-range targets participate in distinct local circuitry is a matter of interest, as the response properties of these cells are likely inherited to some degree from their inputs. Such specific local connectivity of excitatory neurons is present in other sensory areas, such as visual cortex (Ko et al., 2011). Here, excitatory cells that respond to similar visual features such as object orientation are more likely to be connected. In rat, it has further been suggested that M1-projecting neurons are more likely to be aligned with septal instead of barrel regions (Alloway et al., 2004). As barrel and septal-related pyramidal neurons participate in different local circuits (Shepherd and Svoboda, 2005), this may explain differences in their response properties. In contrast, inhibitory interneurons are more likely to be innervated by all local neurons regardless of functional properties (Bock et al., 2011) and, perhaps as a consequence, have less refined receptive fields (Kerlin et al., 2010).

7.2.2 L4 excitatory neurons

The granular layer, L4, defines barrel cortex by its segmentation into dense aggregations of neurons clustered around a hollow. Neurons of septal-related columns above and below L4 are believed to participate in distinct circuits in rats, playing a role in modulation motor output, such as whisking (Alloway, 2008; Alloway et al., 2004). Differences between barrel- and septal-related circuits have received more attention in rat, in part due to the larger size of the septa and the increased ease of identifying and recording from neurons there. The granular cells of the barrel proper are subdivided into at least three distinct cell types, including L4 stellate cells, L4 star pyramids, and L4 pyramidal cells based on morphology and arborization pattern (Staiger et al., 2004). L4 stellate cells are the most numerous (~58%), and other types are less frequently encountered (L4 star pyramids ~25% and L4 pyramidal cells ~17%). L4 stellate cells confine their dendrites almost exclusively to L4, and their axonal projection similarly is well restricted to L4 and the supragranular layers but does not extend to L1. Thus, stellate cells anatomically demonstrate the general connectivity theme: strong within-layer connectivity to other L4 cells (Feldmeyer et al., 1999) and strong ascending connectivity with L3 (Feldmeyer et al., 2002; Lefort et al., 2009). L4 star pyramids also project to L3, although this projection is less restricted to the same barrel column, spreading horizontally by one or two adjacent barrel columns. L4 pyramidal cells target both L3 and L5 and have horizontal arborizations that extend into adjacent barrel columns as well. All three types are recipients of thalamic innervation (Staiger et al., 2004). Thalamocortical innervation canonically arrives in L4 of the cortex, and its effect is amplified via particularly strong local connectivity between excitatory cells (Bruno and Sakmann, 2006). Runaway excitation may be limited by strong disynaptic inhibition from L4 parvalbumin-expressing (PV+) fast-spiking (FS) neurons, which are also targeted by incoming VPM axons (Cruikshank et al., 2007, 2010). L4 somatostatin-expressing (SST+) neurons, while not strongly excited by VPM input, can disinhibit L4 excitatory cells by inhibiting L4 PV+ neurons (Xu et al., 2013). Thus, excitation might enter cortex via L4 and be passed on to supragranular layers (and, to a lesser extent, infragranular layers). This canonical pathway is not the exclusive thalamic pathway within barrel cortex, as it seems L5 in some cases may actually respond to incoming touch information more rapidly than L3 (O'Connor et al., 2010), potentially due to direct thalamic activation of L5 neurons (Constantinople and Bruno, 2013). As described earlier, VPM axons arborize not only in L4 but also at the L5/6 border.

7.2.3 Infragranular excitatory neurons

The infragranular layers have a rich variety of cell types. The cell-type variation in L5 has been appreciated for a long time, but more recently transgenic lines have been developed that enable the targeting of specific cortical layers in mouse (Gerfen et al., 2013). Reconstructions of the long-range projections of single neurons (Economo et al., 2016) may soon provide a window into the full diversity of cortical pyramidal cells. Without a finely detailed survey of the variety of axonal projections, L5 excitatory cell types can generally be divided into two classes: thick-tufted neurons and thin-tufted neurons (Shepherd, 2013). Thick-tufted neurons may also be called pyramidal tract type (PT type) on the basis of their projections to subcortical targets, including thalamus, superior colliculus, brain stem, and the corticospinal tract in some cases. While their axons pass through the internal capsule, they send a collateral to ipsilateral striatum. They are found exclusively in L5B. These cells are intrinsic bursting neurons. While they have been hypothesized to target multiple subcortical regions (Kita and Kita, 2012), evidence from other cortical areas suggests that there are subtle differences within PT-type cells, which vary with their long-range target (Rojas-Piloni et al., 2017). Some may specifically target thalamus and pons (Economo et al., 2017). In contrast, the thin-tufted cells are called intratelencephalic (IT type). These target exclusively ipsilateral and contralateral cortex and striatum, although single neurons may target a subset of these structures. These are found in both L5A and L5B, although there is likely to be some variation in local and long-range connectivity across L5A and L5B. IT-type and PT-type L5 neurons participate in similar general patterns of cortical connectivity, receiving input from L2/3. More superficial L5 neurons receive greater input from L2, whereas deeper L5 cells receive more input from L3 (Hooks et al., 2011; Lefort et al., 2009). Although it is unknown for barrel cortex, studies in other cortical areas suggest that IT-type and PT-type neurons participate in distinct local circuits (Schubert et al., 2001). IT-type cells send output to other IT-type cells and PT-type cells, but PT-type cells do not project back to IT-type cells (Anderson et al., 2010; Kiritani et al., 2012). In this model, corticofugal output neurons—neurons whose signal is relayed to subcortical structures—accumulate information from other neurons and transmit a signal out of cortex.

Pyramidal neurons of L6 include multiple subtypes, but the most prominent types are corticothalamic and corticocortical neurons. L6 is relatively cell dense and thick, which means a potentially large number of neurons involved in local circuit processing. During behavior, however, L6 pyramidal neurons fire action potentials at relatively low rates, thus

making their contribution to cortical processing less easy to discern. One of the earliest cell-type specific pyramidal cell lines generated for cortex, the Cre-driver mouse line Ntsr1_GN220 (Gerfen et al., 2013) was used to test circuit connectivity in S1. This line labeled only corticothalamic neurons and was initially proposed to have a role mediating cortical gain in primary visual cortex (Olsen et al., 2012). Furthermore, L6 corticothalamic neurons may specifically target L5A pyramidal cells in an ascending pathway to affect cortical output to other targets, including corticocortical and corticostriatal outputs (Kim et al., 2014).

7.2.4 Inhibitory neuron connectivity

The local connectivity of cortical GABAergic neurons has been more difficult to describe given the large number of inhibitory cell types (Petilla Interneuron Nomenclature et al., 2008). A few general principles have been elucidated. First, there are three large classes of interneurons, each marked by expression of a single gene (Fig. 7.4). These are PV, SST, and 5-HT_{3A} receptor (5-HT_{3A}R) (Lee et al., 2010; Tremblay et al., 2016). PV+ interneurons include both basket cells, which target the perisomatic region of pyramidal neurons, and chandelier cells, which target the initial segment of pyramidal neuron axons. PV+ interneurons exhibit FS during single unit recordings. They receive input from cortical and thalamic sources, and both their input and output show synaptic depression (Beierlein et al., 2003; Gupta et al., 2000). SST+ interneurons include Martinotti and (more rarely) non-Martinotti subtypes. Martinotti cells have axons that target L1 dendrites of pyramidal neurons and are often low-threshold spiking (LTS) cells. Their inputs and outputs both show synaptic facilitation. A small subset of SST+ neurons may be FS. The 5-HT_{3A}R+ interneurons are heterogeneous. About half of these cells are vasoactive intestinal peptide (VIP)−expressing interneurons, which play a specialized role in disinhibition (Lee et al., 2013; Pfeffer et al., 2013). Non-VIP+ 5-HT_{3A}R+ cells include single bouquet cells (SBCs) and neurogliaform cells (NGFCs). Inhibitory neurons are not distributed uniformly throughout barrel cortex but have a characteristic laminar distribution, with 5-HT_{3A}R+ interneurons making up almost all of the L1 GABAergic interneurons and about half of those in L2/3. 5-HT_{3A}R+ interneurons are rare in deeper layers. PV+ and SST+ interneurons are generally absent from L1 and make up roughly even numbers of L5/6 cells. PV+ interneurons are present in greater numbers than SST+ cells in L4. Consistent with this, PV+ cells provide strong feedforward inhibition to L4 stellate cells following corticothalamic excitation from VPM. Both are present in L2/3. The excitatory inputs to interneurons have been studied for a large number of cells in L2/3 of S1 (Xu and Callaway, 2009). All cell types studied receive excitatory within-layer input from pyramidal cells. Some subsets also received translaminar input from L4 or L5A.

The arrangement of feedforward inhibitory networks has been the subject of great interest from anatomists, physiologists, and computational modelers due to the morphological variety of axon and dendritic arborizations, the distinct pharmacology and excitability of its component neurons, and its key role in balancing the network. As one simplifying principle, it is clear that for every layer of neocortex, the strongest source of inhibitory input to pyramidal neurons originates from within the same layer (Katzel et al., 2011). It is further suggested that both SST+ and PV+ interneurons

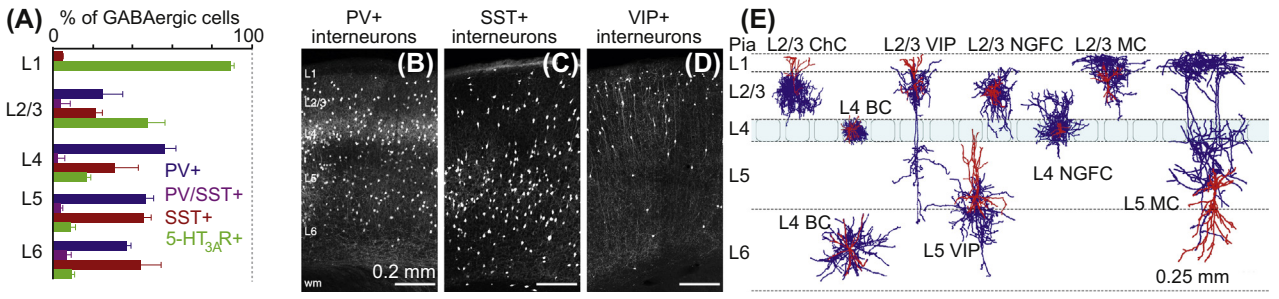

FIGURE 7.4 **Three major populations of GABAergic cortical interneurons.** (A) The percent of neurons expressing one of three markers for the major classes of cortical interneurons (PV, SST, and 5-HT_{3A}R), plotted as a function of cortical layer in S1. A small population expresses PV and SST (purple). (B−D) Images showing the distribution of three populations (PV, SST, VIP) for which Cre driver lines exist. L1 at top. (E) Example reconstructions of several types of cortical interneurons. Dendrites are shown in red, and axons are shown in blue. PV+ subtypes include the axon initial segment-targeting chandelier cells (L2/3 ChC), as well as the more numerous basket cells (L4 BC and L6 BC). 5-HT_{3A}R+ subtypes include VIP+ interneurons (L2/3 VIP and L5 VIP) as well as neurogliaform cells (L2/3 NGFC and L4 NGFC). SST+ interneurons include L1 targeting Martinotti cells (L2/3 MC and L5 MC). *ChC*, chandelier cell; *PV*, parvalbumin; *SST*, somatostatin; *VIP*, vasoactive intestinal peptide. *(A) Based on Lee, S., Hjerling-Leffler, J., Zagha, E., Fishell, G., Rudy, B., 2010. The largest group of superficial neocortical GABAergic interneurons expresses ionotropic serotonin receptors. J. Neurosci. 30, 16796−16808; (B−E) From Feldmeyer, D., Qi, G., Emmenegger, V., Staiger, J.F., 2018. Inhibitory interneurons and their circuit motifs in the many layers of the barrel cortex. Neuroscience 368, 132−151.*

connect to at least half and potentially all excitatory cells of the local circuit, providing a blanket of inhibition (Fino et al., 2013; Fino and Yuste, 2011; Packer and Yuste, 2011). This does not fully account for differences in the gain of inhibition, differences in the subtype of interneuron providing the inhibition, or differences in the overall effect depending on the dendritic subdomain targeted. It is likely that there is more to understand given the highly specific targeting of basket cell axons (to the soma) and Martinotti cells (to the apical dendrites). One well-characterized motif is the feedforward inhibition in L4 of barrel cortex. Following VPM input that excites the well-connected excitatory network of spiny stellate cells, FS PV+ interneurons are also excited and act to limit runaway excitation of this input layer (Cruikshank et al., 2007). SST+ interneurons are poorly excited except during trains of activity (Beierlein et al., 2003).

More recently, the local network of inhibitory connectivity has been characterized in visual and somatosensory cortex. Connectivity studies show that PV+ and SST+ interneurons are positioned to inhibit pyramidal neurons (Fig. 7.6). SST+ interneurons also inhibit PV+ neurons, whereas VIP+ neurons are specialized to inhibit SST+ neurons. This suggests a disinhibitory model in which VIP+ neuron activation inhibits SST+ neurons, thus disinhibiting PV+ and pyramidal neurons (Pfeffer et al., 2013). This has been suggested as one means by which focal disinhibition could be achieved during network operation. But what is the signal that activates VIP+ cells? In vivo studies of somatosensory cortex during whisking suggest that SST+ neurons are tonically active but are transiently silenced during touch. At the same time, excitability of PV+ cells and pyramidal cells is increased. Putative VIP+ neurons are also excited at this time (Gentet et al., 2012). M1 projections to S1 are capable of specifically exciting VIP+ neurons, suggesting that this disinhibitory microcircuit is activated by motor signals (Lee et al., 2013). A similar disinhibitory motif involving VIP neurons has been proposed in frontal cortex and visual cortex (Fu et al., 2014; Pi et al., 2013), although the nature of the afferent that activates VIP+ neurons may differ across cortical areas.

7.2.5 Corticothalamic and corticocortical inputs

Ascending thalamocortical input to barrel cortex has been well studied, but retrograde label reveals a range of corticocortical inputs (Fig. 7.5). These include motor inputs from the whisker region of M1, other regions of somatosensory cortex including S2, and contralateral S1, among others. With the emergence of optical methods of specifically exciting afferents from defined neuronal population (such as excitation of corticocortical or corticothalamic afferents that express channelrhodopsin-2 [ChR2] following viral transfection) (Boyden et al., 2005; Nagel et al., 2003; Petreanu et al., 2007, 2009), these long-range inputs can be mapped and quantitatively compared. Input from the thalamus, although previously studied with conventional approaches, has also been investigated with optogenetic methods (Cruikshank et al., 2010). Corticothalamic pathways representing different aspects of incoming somatosensory information and targeting different layers originate from two thalamic nuclei. The lemniscal pathway originates from VPM thalamus and is the primary source of direct somatosensory input to thalamus. The paralemniscal pathway originates from the medial subdivision of the posterior nucleus of thalamus (POm) and is traditionally thought of as a higher-order somatosensory input to cortex. Thus, the degree to which these pathways remain segregated and where this information again converges to alter the S1 representation of touch is of some interest. It has been proposed that L5A neurons represent the first station of such integration, because they are positioned to receive both particularly strong POm input (Bureau et al., 2006; Petreanu et al., 2009) as well as the descending excitatory output from L4 (Schubert et al., 2006). VPM input, as expected, most strongly excites L4 but does provide some input to L3 and L5. POm input is remarkably precise in targeting L5A, where POm axons arborize extensively (Petreanu et al., 2009). The same afferents also arborize in layer 1 and may target cell types where quantification of the input is more challenging because of its distance from the soma. Inputs from contralateral S1, at least those originating from L2/3 neurons, target L2/3 and L5, which is a similar laminar pattern of output as the ipsilateral projections of these cells within the local column (Petreanu et al., 2007). S2 also provides feedback to S1 (Minamisawa et al., 2018), although the laminar targeting has not yet been quantified to the same extent. The feedback projection from M1 arborizes in L1 as well as the infragranular layers. It targets pyramidal cells, PV+ interneurons, and SST+ neurons of the infragranular layers (Kinnischtzke et al., 2014). This is consistent with a corticocortical hierarchy in which feedforward output (from primary sensory areas, for example) excites the upper layers of cortical areas they target, such as L2/3 and L5A in M1 (Mao et al., 2011), whereas the corticocortical feedback from hierarchically higher areas targets deeper layer cells.

Collectively, then, the past century and more of investigations has taught us much of what the basic cell types are in different layers of barrel cortex. There is still much to be learned about the connectivity of different cell types, especially as it becomes possible to trace the axons of single neurons throughout the whole brain. We furthermore have an understanding of their general patterns of local excitatory connectivity and are beginning to integrate local circuit interneurons into this understanding. Long-range inputs are almost exclusively excitatory and are being included in this further

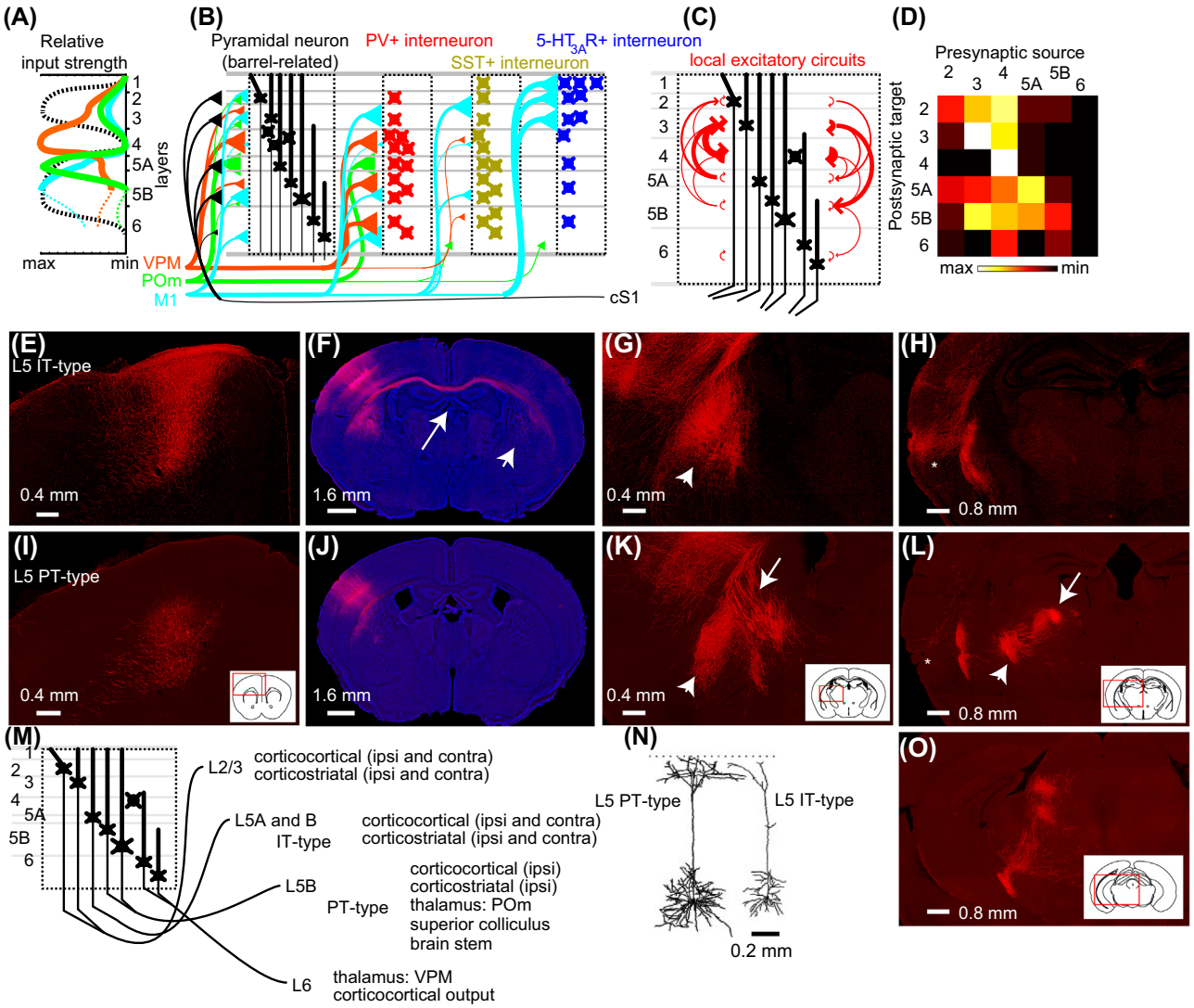

FIGURE 7.5 **Local and long-range excitatory connectivity.** (A) Long-range excitatory input to primary somatosensory cortex (S1) targets excitatory cells in different layers to different degrees. Feedforward excitation from thalamus (VPM, orange) excites L4 most strongly, whereas POm excitation (green) specifically targets L5A. Primary motor cortex (M1) excites L5 strongly. Contralateral S1 (cS1, black) excites L2/3 and L5 similarly. (B) The same excitatory inputs target interneurons in different layers. PV interneurons (red) receive substantial VPM, PO, and M1 input, especially in infragranular layers. SST+ neurons in L2/3 and L5 receive M1 input. The VIP+ subset of 5-HT_{3A}R+ neurons in L2/3 receive strong M1 input. This presentation is selected to emphasize differences in laminar targeting depending on the interneuron subtype. (C) The local circuit is characterized by strong ascending connections from L4 to L3 as well as some L5 to L2/3 input. The strongest descending pathway is L2/3 to L5. The connectivity matrix (derived from whole cell—paired recordings) shows similar connectivity with strong within-layer connections in L4 and L3. (E—O) The long-range output from S1 varies strongly with pyramidal cell type. Images contrast the long-range projections from two major types of cells in L5, the IT type (intratelencephalic, which reside in L5A and L5B) and PT type (pyramidal tract type, residing in L5B exclusively). (E, I) IT-type axons are much stronger to corticocortical targets such as M1. Inset shows location of images in cartoon of coronal section. (F, J) The injection site in S1 is well labeled for both cell types, but IT-type neurons cross the midline (*arrow*) and arborize in contralateral cortex and striatum (*arrowhead*). Neurotrace Blue, a fluorescent Nissl stain, is used to show overall structure. (G,K). Ipsilateral striatal targeting (*arrowhead*) is present for both IT-type and PT-type L5 neurons. Thicker myelinated fibers of passage pass through striatum (*arrow*). (H,I) PT-type, but not IT-type, axons target subcortical structures such as thalamus. *Arrowhead* indicates L5 input to POm, although axons pass through VPM. Axons can be seen descending in the internal capsule (*arrowhead*). Corticocortical output to higher-order cortex, such as ectorhinal areas, is much stronger from IT-type (*asterisk*) than PT-type axons. (M) Cartoon summarizing the long-range outputs of excitatory S1 neurons. L4 omitted due to principally providing local output. (N) Differences in thick-tufted (left) and thin-tufted (right) neurons in barrel cortex. Thick-tufted neurons are also intrinsic bursting cells. This subtype corresponds to PT-type L5B neurons. Thin-tufted cells are regular spiking cells. This subtype corresponds to IT-type neurons. (O) The PT-type projection is present in brain stem structures, including superior colliculus. *POm*, posterior nucleus of thalamus; *SST*, somatostatin; *VPM*, ventroposteromedial. *(C) From Hooks, B.M., Hires, S.A., Zhang, Y.X., Huber, D., Petreanu, L., Svoboda, K., Shepherd, G.M., 2011. Laminar analysis of excitatory local circuits in vibrissal motor and sensory cortical areas. PLoS Biol. 9, e1000572; Lefort, S., Tomm, C., Floyd Sarria, J.C., and Petersen, C.C., 2009. The excitatory neuronal network of the C2 barrel column in mouse primary somatosensory cortex. Neuron 61, 301—316; (E, I) From Paxinos and Franklin (2004).*

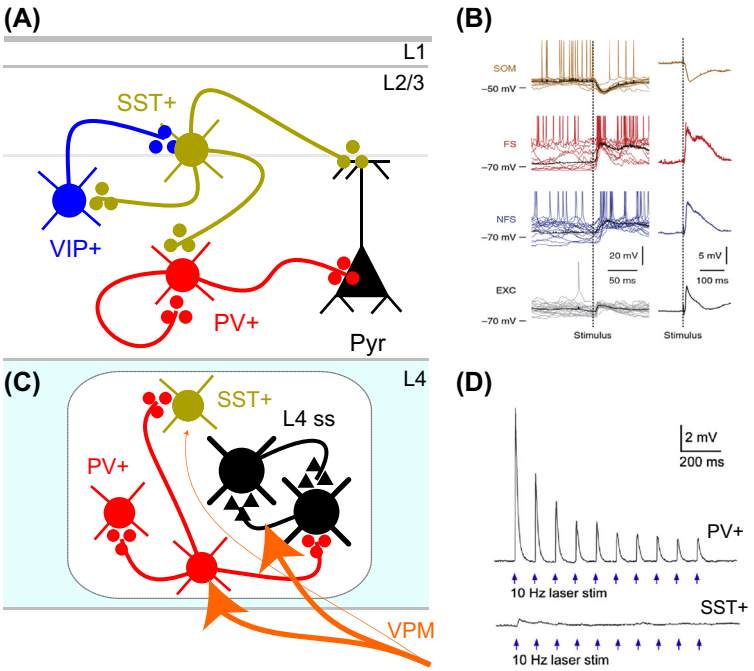

FIGURE 7.6 Local circuitry for inhibition and disinhibition. (A) The circuitry underlying disinhibition of pyramidal neurons is hypothesized to originate from VIP+ interneurons (blue), a subset of $5HT_{3A}R$+ interneurons. These inhibit SST+ cells (gold), which in turn disinhibit pyramidal neurons (black) and PV+ interneurons (red). Primary motor cortex (M1) provides one signal that may activate VIP+ interneurons. (B) In vivo responses to whisker touch in L2/3 are strongly modulated by cell type. Tonic activity in SST+ interneurons (gold) is reduced, whereas firing is enhanced in PV+ interneurons (red) and non-SST+ regular spiking interneurons (blue). L2/3 pyramidal neurons also depolarize (black). (C) Feedforward excitation from thalamus (VPM, orange) excites L4 spiny stellate cells (L4 ss, black) and PV+ interneurons (red), but not SST+ interneurons (gold). (D) In vivo response to optogenetic stimulation of thalamic input induces large postsynaptic potential in PV+ interneurons, but not in SST+ interneurons. *PV*, parvalbumin; *SST*, somatostatin; *VIP*, vasoactive intestinal peptide; *VPM*, ventroposteromedial. *(A) From Pfeffer, C.K., Xue, M., He, M., Huang, Z.J., Scanziani, M., 2013. Inhibition of inhibition in visual cortex: the logic of connections between molecularly distinct interneurons. Nat. Neurosci. 16, 1068–1076; (B) From Gentet, L.J., Kremer, Y., Taniguchi, H., Huang, Z.J., Staiger, J.F., Petersen, C.C., 2012. Unique functional properties of somatostatin-expressing GABAergic neurons in mouse barrel cortex. Nat. Neurosci. 15, 607–612; (C, D) From Cruikshank, S.J., Urabe, H., Nurmikko, A.V., Connors, B.W., 2010. Pathway-specific feedforward circuits between thalamus and neocortex revealed by selective optical stimulation of axons. Neuron 65, 230–245.*

understanding. From a systems perspective, studies have also begun to describe the receptive fields of whisker touch. Associating neural response to stimuli with an understanding of the underlying circuits would be a great advance in clarifying how connectivity results in different response properties of different cells. However, connectivity studies also often lack the ability to describe how connectivity might change during realistic spike trains, integrating short-term plasticity into the map. Furthermore, except for paired recordings at short distances, circuit studies are often exciting large numbers of afferents together and thus not in quite the spatial and temporal pattern in which inputs are active under physiological conditions. Nonetheless, the substantial efforts of many research groups have combined to give a reasonable understanding of the circuitry of barrel cortex. In the sections that follow, we will describe how this circuitry is formed during development and how it responds to different patterns of sensory experience.

7.3 Connections during birth and migration

As in other cortical areas, the principal excitatory neurons of somatosensory cortex are generated by progenitor cells in the ventricular and subventricular zones. Nascent neurons migrate outward, initially forming the subplate and then the neocortical layers. The timing of birth determines to a great extent the layer to which the neuronal somata will migrate (Rakic, 1974). The earliest born neurons form the deeper layers, with later-born neurons migrating past them to form more superficial layers. As migration at this stage is largely radial, neurons of this radial column form a fundamental building block of cortical columns (Mountcastle, 1997; Rakic, 1988).

Circuit formation has already begun at this time. The "radial unit hypothesis" (Rakic, 1988) suggests that these units might participate in a form of lineage-dependent circuit formation. Transient electrical synapses through gap junctions connect neurons derived from the same radial glial progenitors, enhancing synchronous activity between roughly postnatal

day (P)1 and P6 in mouse. Prior gap junction coupling contributes to preferential connectivity of sister neurons in individual radial clones that emerge at later developmental times (P10–P21) (Yu et al., 2009, 2012b). This phenomenon lays down the general outline of local excitatory circuit formation. In contrast, GABAergic interneurons are born outside the local circuit in the ganglionic eminences of the subventricular zone and migrate tangentially into neocortex. The medial, lateral, and caudal ganglionic eminences produce distinct subtypes of GABAergic neurons (Butt et al., 2005; Xu et al., 2004). The migrating neurons are then widely dispersed and integrated into local circuitry across cortex (Harwell et al., 2015; Mayer et al., 2015; Walsh and Cepko, 1992). The birth date of inhibitory neurons also determines the laminar location of their somata, with early-born cells found in the deeper layers, whereas later-born cells are found in superficial layers (Fairen et al., 1986; Valcanis and Tan, 2003).

7.4 Thalamocortical innervation

In mature mammals, two major principal thalamic nuclei innervate primary somatosensory cortex. The primary sensory input originates via the ventroposterolateral (VPL) and VPM nuclei of thalamus, sometimes collectively termed the ventrobasal complex (Rose and Mountcastle, 1952), which represent sensory information from the body and face, respectively. This pathway is called the lemniscal pathway. These afferents arborize in and target predominantly L4, with a smaller terminal arborization at the border of L5B and L6 (Cruikshank et al., 2010; Wimmer et al., 2010b). Principal thalamic input to L4 is a prominent feature of input to visual and somatosensory cortex.

Individual thalamocortical axons target single barrels and represent touch information with great specificity: for example, touch of a single whisker (Diamond et al., 1992). This input, deriving from the medial lemniscus-recipient VPM, is thus referred to as the lemniscal pathway in rodents (Feldmeyer, 2012). In rodents, a higher-order thalamic region, the medial portion of the POm, also provides sensory information to cortex (Jones and Diamond, 1995). In contrast to the VPM input, this is called the paralemniscal pathway. Terminal arborizations are prominent in L1 and L5A, and individual axons have relatively broad arbors (Ohno et al., 2012). POm afferents respond to broader somatic receptive fields, such as multiwhisker responses (Diamond et al., 1992). Additional ascending pathways, such as the extralemniscal pathway via ventrolateral VPM, have more diffuse cortical targets and have received less attention (Bokor et al., 2008; Pierret et al., 2000).

During development, thalamic axons from VPM reach the intermediate zone under the cortical plate before birth. Axonal projections remain in the subplate until after their targets have completed migration (Rakic, 1977; Shatz and Luskin, 1986). Thalamic connections to subplate form during this time. Thereafter, thalamic axons extend to form dense arborizations in L4 and L6 (Catalano et al., 1991), with further branching within L4 (but not tangentially) during the week following birth (Catalano et al., 1996). This suggests that axons grow progressively and remain spatially restricted. Although some systems, such as retinal inputs to thalamus and superior colliculus, establish topographic representations by initial exuberant axonal arborization that is later pruned into topographically appropriate areas (Shatz and Stryker, 1988), the thalamic innervation of cortex seems to proceed in a more spatially restricted manner, implicating a role for activity-independent mechanisms in the laying down of an initial, coarse map (Cang and Feldheim, 2013).

Activity-dependent mechanisms play a substantial role in the development of these systems. Subplate neurons, a predominantly transient population that resides just below the developing cortical plate, play a key role in the anatomical and functional maturation of thalamic input to L4 neurons in sensory cortex. Selective ablation of these cells results in appropriate thalamocortical projections failing to form both anatomically (Ghosh et al., 1990) and functionally (Kanold et al., 2003). Some subplate neurons receive synaptic input from thalamic afferents (Friauf et al., 1990). These cells in turn have axons that project to the developing cortex, positioning subplate neurons to boost thalamic signals to L4 neurons during early developmental stages (Allendoerfer and Shatz, 1994). As early as E17, subplate neurons may extend axons into the L4 barrels, which persist during the first postnatal week, but these axons are eliminated during the second postnatal week (Pinon et al., 2009). Notably, subplate neurons also extend axons to the thalamus and may thus lay down the early stages of the corticothalamic output (De Carlos and O'Leary, 1992; McConnell et al., 1989). Subplate neurons are then eliminated by apoptosis perinatally (Valverde and Facal-Valverde, 1987).

Increases in synaptic strength of thalamocortical inputs to excitatory L4 neurons in somatosensory cortex occur over the first week following arrival of axons in cortex, occurring at P2–P10 in mice. These connections initially include "silent synapses"—synapses where transmission is not detectable by conventional recording techniques at negative resting membrane potentials, but which can be converted to functional synapses during development. Silent synapses appear quiet during transmitter release since they contain only the *N*-methyl-D-aspartate receptor (NMDAR) subtype of glutamate receptors (a tetramer that includes obligatory subunit GluN1 and subunits GluN2A and GluN2B). These receptors require depolarization to pass current (Isaac et al., 1995). Recordings at depolarized potentials show that these synapses exist at

early ages. Silent synapses are then developmentally converted to more functional connections. Silent synapses cease to be present at about the same developmental time point when long-term potentiation (LTP) becomes difficult to induce by thalamic stimulation (Isaac et al., 1997). This conversion from functionally silent to active synapses is mediated by insertion of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) at synapses (Malinow and Malenka, 2002). AMPARs are a distinct ionotropic subtype of glutamate receptor (a tetramer whose subunits include GluA1, GluA2, GluA3, and GluA4). For barrel cortex, LTP-dependent strengthening occurs specifically in thalamocortical inputs to L4, as thalamocortical input to L6 neurons do not strengthen during this time (Crocker-Buque et al., 2015).

What about thalamocortical innervation of inhibitory interneurons? At comparable ages (P3 in rodents), thalamic inputs do not yet excite local circuit interneurons (Daw et al., 2007). Cortical interneurons include three major populations: PV-expressing cells, SST-expressing cells, and 5-HT_{3A}R (a serotonin receptor subunit)-expressing cells (Lee et al., 2010). PV+ neurons are generally FS cells, whereas SST+ interneurons are often called LTS neurons. These early studies have focused on input to PV+ cells, since they were most readily identifiable by their FS phenotype. The effect of $GABA_A$ receptor ($GABA_AR$) activation begins to change about this age in neocortex, as internal [Cl^-] changes. Very early in development, $GABA_AR$ activation is depolarizing. A gradual reduction in $[Cl^-]_i$ occurs prior to birth, but during the first one or two postnatal weeks, $[Cl^-]_i$ rapidly decreases, lowering the $GABA_AR$ reversal potential to adult levels (Owens et al., 1996). But as the inhibitory input to excitatory neurons matures, similarly, thalamic excitation to GABAergic neurons, especially PV+ cells, also increases (Daw et al., 2007). Overall, feedforward inhibition is strengthened, as unitary inhibitory connection strength as well as connection probability increases to L4 excitatory cells (Daw et al., 2007). This later development of feedforward inhibition, starting at P6−7 in mice, allows time for excitatory synaptic development (from P2) without inhibitory attenuation from FS cells.

In contrast to the developmental trajectory of thalamic input to L4 PV+ cells, input to SST+ neurons has received less attention. SST+ neurons in the mature circuit are known to receive less thalamic input than either excitatory cells or PV+ neurons (Cruikshank et al., 2007, 2010). However, it is interesting to note that in infragranular layers, thalamic inputs are capable of exciting SST+ neurons as early as P6, and this excitation decreases developmentally (Tuncdemir et al., 2016). This indicates that SST+ neurons in other layers might be targeted by thalamic inputs earlier, although this is unknown.

7.5 Developmental critical periods and barrel formation in the somatosensory system

7.5.1 Formation of barrels

Positioning of the somatosensory cortex along the anterior/posterior axis is regulated by growth factors. Embryonic reduction in FGF8 leads to the shift of the barrel field more anteriorly while overexpression moved it posteriorly. Thus, the amount and location of FGF8 expression appear to be critical in determining proper localization of the barrel field (Fukuchi-Shimogori and Grove, 2001). Formation of the barrels themselves begins postnatally. Over the first 4−5 postnatal days, thalamocortical axons cluster into barrels (Erzurumlu and Jhaveri, 1990), and L4 excitatory neurons form the cell-dense barrel walls enclosing cell-sparse barrel hollows (Rice et al., 1985). VPM axons target the appropriate L4 barrel and develop an elaborate axonal arborization during the first postnatal week without exuberant growth and pruning in adjacent barrels (Agmon et al., 1993, 1995). Innervation by thalamocortical axons initially targets the border of L5/6 as well as L4 (Catalano et al., 1991).

Disruption of axonal growth and arborization could contribute to failure of normal circuit formation. Axonal growth is disrupted by deficits in synaptic transmission affecting either pre- or postsynaptic neurons. Growth of these axons is indeed disrupted in the mouse mutant *barrelless*, which lacks cytoarchitectural markers of barrels due to disruption of the adenylate cyclase 1 (*ADCY1*) gene (Abdel-Majid et al., 1998; Welker et al., 1996). If *ADCY1* is selectively disrupted exclusively in cortex, barrels are present, indicating a role of *ADCY1* expression in ascending relays such as thalamus (Abdel-Majid et al., 1998). In *barrelless* mice, axons remain in the appropriate layers but arborize much more broadly across L4 and L5/6, disregarding barrel boundaries. Deletion of RIM1 and RIM2 (which are involved in vesicular fusion) in the thalamus also leads to disruption in neuronal density between the barrel hollow and barrel wall, which resembles the *barrelless* phenotype. However, specific deletion in the cortex did not disrupt barrel formation, again implicating thalamocortical and not corticocortical transmission in normal barrel formation (Narboux-Neme et al., 2012). In addition to NMDAR, knockout of metabotropic glutamate receptor 5 (mGluR5) and its downstream target, phospholipase C-β1(PLC-β1), interferes with axonal innervation from thalamus, thus disrupting the formation of the barrel pattern (Hannan et al., 2001). Thus, normal synaptic input from thalamus appears to be important for normal anatomical development.

Some postsynaptic deficits cause a specific loss of barrels without gross abnormality in thalamic innervation. Exuberant growth outside of proper targets occurs when postsynaptic NMDARs (via knockout of the obligatory NMDAR subunit GluN1) are not expressed. Axons then branch in inappropriate layers and outside a single barrel (Lee et al., 2005). Altered signaling in the RAS/MAPK and PI3K pathways attenuates barrel formation without major disruption of thalamic innervation, including by disruption of SynGAP (Barnett et al., 2006) and conditional cortex-specific disruption of neurofibromin (Lush et al., 2008). Other signaling pathways, including PKA, are similarly implicated in normal postsynaptic formation of the barrel field (Watson et al., 2006). These examples demonstrate the complexity of molecules that are involved in normal formation of barrels and the importance of glutamatergic signaling and downstream pathways in L4 neurons.

7.5.2 Receptive fields of barrel cortex neurons

The response of barrel cortex neurons to each whisker stimulation is highly selective (Li and Crair, 2011). Most neurons throughout a barrel column respond most strongly and at shortest latency to stimulation of the contralateral principal whisker. For example, neurons in the D1 barrel column will respond mostly strongly to D1 whisker stimulation (Simons, 1985). Many barrel cortex neurons also respond at longer latency to stimulation of individual surround whiskers, with receptive field sizes being larger for subthreshold (Moore and Nelson, 1998; Zhu and Connors, 1999) than for suprathreshold (Armstrong-James and Fox, 1987) responses. The amplitude of synaptic potentials evoked by single whisker stimulation is reduced by about 50% for surround whiskers (Zhu and Connors, 1999). Surround whisker receptive fields arise intracortically via horizontal transmission (Armstrong-James et al., 1991; Fox et al., 2003). Surround whisker stimulation may also cause inhibitory surround suppression, attenuating responses to subsequent principal whisker stimuli (Higley and Contreras, 2005), although individual neuron receptive fields may be quite complex in time and space (Ramirez et al., 2014). Responses to touch can be decoded first in layers 4 and 5 (Constantinople and Bruno, 2013; O'Connor et al., 2010), with high temporal precision in L4 responsiveness (Hires et al., 2015). Because the entire barrel-related column contains neurons sharing responsiveness to the same principal whisker, the strong relationship between this functional unit and individual whiskers in the periphery could be exploited to study the role of activity, experience, and molecular mechanisms on circuit development.

7.5.3 Critical periods for functional connectivity of ascending somatosensory pathways

Elegant studies of visual cortex function during the period shortly after eye opening demonstrated the existence of a developmental critical period for the emergence of normal cortical circuitry and function (Wiesel and Hubel, 1963). The cortical critical period for sensory system development was characterized by several features: (1) Sensory responses required activity and, in particular, appropriate sensory experience during a particular developmental time window for functional properties of the circuit to develop normally (Hensch, 2004). (2) These properties could be perturbed by sensory manipulations, such as sensory deprivation, only during certain "critical" periods of development. (3) After critical period closure, the same manipulations resulted in attenuated or no plasticity. However, sensory responses can be measured in cortex in a variety of ways, such as the suprathreshold response magnitude to ipsilateral and contralateral eye input, the precision of orientation tuning, or the strength of a given synaptic input. Responses can also be measured at different stages in the ascending sensory pathways, each of which may develop at different times. Therefore, it is important to consider that different circuit and response features may show different timing for critical period plasticity (Hooks and Chen, 2006).

The ability to study an anatomical correlate of the body representation in cortex inspired the exploration of the relationship between whisker removal and the corresponding barrel representation. Initial experiments lesioned whisker follicles in P0 mice (Fig. 7.7). 1−2 months later, barrels representing the lesioned whiskers are absent, and surrounding barrels expand to partially fill the vacant cortical area (Van der Loos and Woolsey, 1973). However, this phenomenon is highly age dependent as whisker follicle lesion after P5 does not lead to reorganization of barrels, whereas the degree of barrel shrinkage is progressively reduced with lesions from P0 to P5 (Woolsey and Wann, 1976). More peripheral areas such as brain stem and thalamus show still earlier critical period closure (Durham and Woolsey, 1984). Thus, the ascending somatosensory pathway shows sequential development. If whiskers are plucked rather than the follicles lesioned, barrels corresponding to removed whiskers form normally, with the "spared" barrel being enlarged in only a third of rats (Fox, 1992). Furthermore, whisker trimming from birth had no effect on the barrel map (Simons and Land, 1987), suggesting that deprivation of sensory input alone is insufficient to prevent barrel map formation.

However, the closure of the critical period for the gross formation of the barrel field does not mark the closure of cortical plasticity. Sensory manipulations such as whisker plucking or trimming continue to have effects on circuit

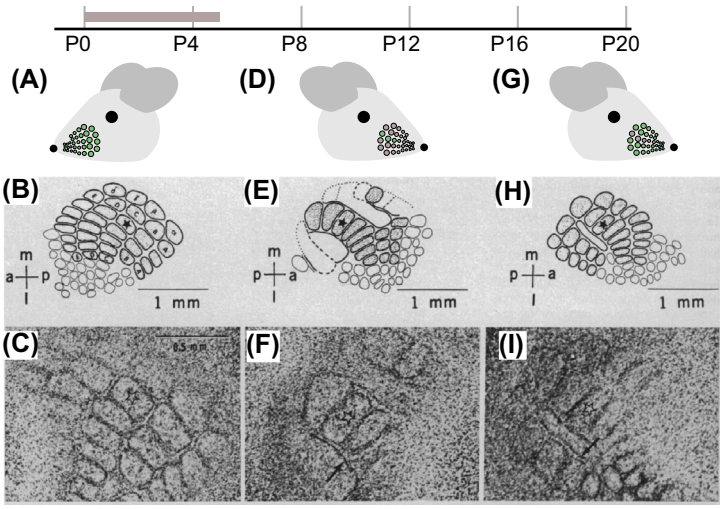

FIGURE 7.7 **Critical period for plasticity of barrel anatomy in response to whisker follicle lesion.** Barrel cortex exhibits long-term gross anatomical changes in response to whisker follicle lesion at birth (on P0). However, past P5, whisker follicle lesion does not lead to changes in the morphology of barrels in the somatosensory cortex. In control animals, all whiskers are represented (A, green). Each barrel is represented in the primary somatosensory cortex as shown in a camera lucida drawing (B) and a Nissl-stained tangential section (C). When all the whisker follicles except for row C and β (green) are lesioned on P0, the remaining whiskers expand their cortical representation (D–F). When the follicles of row C and β whiskers (gray) are lesioned on P0, surrounding barrels expand into the area previously associated with lesioned whiskers (G–I). *From Van der Loos, H., Woolsey, T.A., 1973. Somatosensory cortex: structural alterations following early injury to sense organs. Science 179, 395–398.*

connectivity and responsiveness across a range of developmental periods. Although the influence of experience is attenuated at later developmental time points, some manipulations evoke plasticity even into adulthood. When all but one whisker is removed early during the first postnatal week, the area of L4 driven by stimulation of the remaining whisker enlarges. However, this effect diminishes with whisker removal even later during the first postnatal week (Fox, 1992). Other patterns of whisker removal, such as whisker pairing or chessboard deprivation (removal of alternating whiskers), can still elicit receptive field plasticity of L4 neurons in adolescent rodents (Armstrong-James et al., 1994; Diamond et al., 1993; Wallace and Fox, 1999).

Notably, during the first postnatal week, despite the closure of the critical period for structural plasticity of the barrel map, significant changes in thalamocortical connectivity are occurring. For barrel cortex, the best studied synaptic input is the ascending pathway from VPM to L4. During the first postnatal week (P2–5 in mice), VPM inputs to barrel cortex exhibit silent synapses. Silent synapses are excitatory inputs with NMDAR but no functional AMPAR inserted in the postsynaptic membrane (Fig. 7.8). As described, these excitatory inputs onto the excitatory cells of L4 show robust LTP induction in vitro, along with conversion to functional synapses and enhancement of AMPAR responses (Isaac et al., 1997), a process that is developmentally complete by P8–9. Early NMDAR-mediated transmission is dependent on GluN2B expression, and cortex-specific GluN2B knockout demonstrated that GluN2B is obligatory for normal barrel formation, as its mutation led to structural abnormality in barrel cortex (Iwasato et al., 1997; Kutsuwada et al., 1996). During this time, there is a developmental increase in GluN2A and decrease in GluN2B subunit composition, which speeds the kinetics of NMDAR-mediated currents between P7–P10. In situ hybridization revealed that GluN2B is highly expressed beginning during embryonic development, whereas GluN2A expression is delayed and begins postnatally (Lu et al., 2001). Thalamocortical LTP induction was blocked when GluN2B expression was prevented. Because the longer open time of GluN2B-containing NMDAR might permit greater calcium influx associated with activity-dependent gene transcription, this subunit shift was hypothesized to close the critical period. While maturation of NMDAR-mediated kinetics does depend on the shift in subunit composition, blockade of the normal developmental shift in channel subunits by deletion of the GluN2A subunit did not extend the developmental critical period for thalamocortical LTP in response to whisker removal. This suggested that critical period closure might be due to other factors (Lu et al., 2001). Of further interest, the *barrelless* mutation (disruption of the ADCY1 gene) required presynaptically for barrel formation is also implicated postsynaptically in trafficking of AMPAR. Its absence reduces the ability to evoke LTP and results in immature synapses with reduced AMPAR being maintained, which may contribute to abnormal axonal growth patterns (Lu et al., 2003).

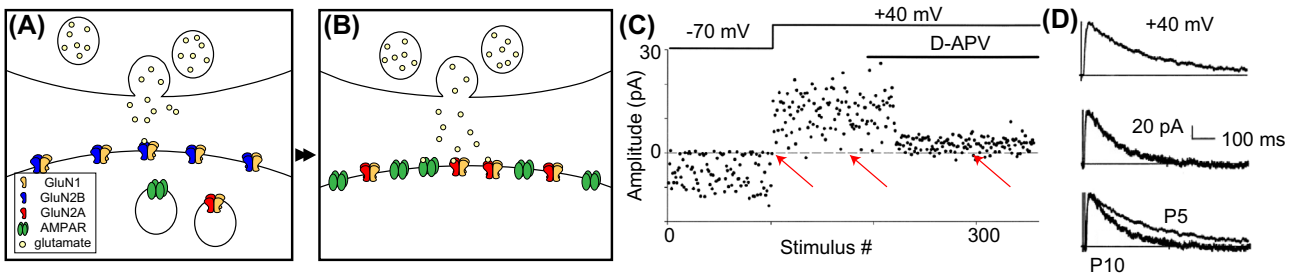

FIGURE 7.8 Mechanisms governing critical period plasticity: changes in AMPAR and NMDAR at synapses. During the first postnatal week, there is a major transition in glutamatergic synapses. Initially, these synapses are silent when recorded at negative potential due to lack of functional AMPAR. Only at depolarized potentials can postsynaptic currents mediated by NMDAR be observed. Early NMDAR synapses predominantly contain GluN2B subunits (A, orange). Around P8–9, the NMDAR component of postsynaptic receptors transitions from a high level of GluN2B to GluN2A (B, red). Concurrently, these synapses become functional after AMPARs are trafficked into the postsynaptic membrane (B, green). This converts silent synapses to mature synapses. (C) Evidence for silent NMDAR-only synapses includes the high failure rate (*red arrow*) of synaptic transmission at −70 mV (when only AMPAR can pass current). Failure rates at young synapses (P4) are reduced during recording at +40 mV, when NMDARs can also pass current. The failure rate increases when NMDARs are blocked with a specific antagonist (D-APV). (D) A further physiological maturation is the shift from kinetically slower GluN2B (at P5) to faster GluN2A-containing NMDAR at P10. *(C) From Isaac, J.T., Crair, M.C., Nicoll, R.A., Malenka, R.C., 1997. Silent synapses during development of thalamocortical inputs. Neuron 18, 269–280; (D) From Lu, H.C., Gonzalez, E., Crair, M.C., 2001. Barrel cortex critical period plasticity is independent of changes in NMDA receptor subunit composition. Neuron 32, 619–634.*

This change in the ability to evoke LTP describes synapse-specific changes in monosynaptic input strength, where specific connections might be enhanced when presynaptic neurons cause postsynaptic ones to fire (Hebb, 1949; Katz and Shatz, 1996). A straightforward interpretation suggests that sensory experience during development excites ascending thalamic axons, allowing strengthening to occur at the VPM to L4 synapse. This change is synapse-specific (sometimes called homosynaptic) plasticity, as it is thought to be caused by the activity patterns of the pre- and postsynaptic neurons, including the relative spike timing (Dan and Poo, 2004). In parallel with this homosynaptic plasticity, homeostatic plasticity provides a mechanism for globally increasing or decreasing the activity of a neuron (Turrigiano et al., 1998; Turrigiano and Nelson, 2004). This can occur either via scaling the overall strength of all excitatory or inhibitory inputs to a neuron or by altering the intrinsic excitability of individual neurons, such as by adjusting voltage-gated conductances.

7.5.4 Intracortical excitatory plasticity

While thalamic inputs are likely of considerable importance in defining the receptive fields of barrel cortex neurons, the number of thalamocortical synaptic contacts is actually quite low, representing only 10%–20% of excitatory synapses (Benshalom and White, 1986). This places local L4–L4 excitatory connectivity in a crucial position to amplify incoming sensory signals. Consistent with this, recordings of unitary synaptic connections suggest that simultaneous activation of multiple L4 neurons may be required to excite individual L2/3 pyramidal neurons (Feldmeyer et al., 2002). The targets of these axons, predominantly L4 spiny stellate cells, have dendrites directed toward the barrel hollow, a structural bias that develops due to differences in both dendritic growth and dendritic regression (Greenough and Chang, 1988). This process also depends on neural activity and requires NMDAR signaling in the L4 stellate cell to stabilize dendritic branches (Mizuno et al., 2014).

Feedforward output connectivity from the L4 barrel to L2/3 develops with a monotonic increase in synaptic input strength during the second postnatal week (Bureau et al., 2004). Concomitantly, the proportion of GluN2B-containing NMDAR decreases, resulting in faster NMDAR-mediated currents; these changes are prevented by whisker plucking from P6 (Mierau et al., 2004). L4 axons are mostly restricted to the column associated with their home barrel, with modest collaterals in adjacent barrel columns (Lubke et al., 2000; Petersen and Sakmann, 2000). Mature axon topography seems to be achieved by an increase in the density of within-column arborization, which seems to complete maturation prior to P30 (Bender et al., 2003). This differs slightly from the exuberant growth and subsequent pruning that characterizes other long-range projections in the nervous system such as at neuromuscular junctions (Buffelli et al., 2003) or retinal inputs to thalamus and superior colliculus (Hong and Chen, 2011). Furthermore, development of the columnar topography of L4 excitatory axons is unaffected by whisker plucking from P8 (Bender et al., 2003), suggesting that it occurs independent of sensory experience.

Whisker receptive fields of L2/3 neurons develop rapidly under normal conditions, shifting from scarcely detectable to mature over a period of about 2 days (P12–P14), at an age when L4 receptive fields are already mature (Stern et al., 2001).

Whisker deprivation before P14 disrupts receptive field maps in L2/3 but not L4, suggesting that the critical period for L2/3 plasticity is later than for L4. The timing of this critical period coincides with the experience-dependent maturation of intrinsic properties and firing patterns, dendritic structure, and spine motility of L2/3 pyramidal neurons (Lendvai et al., 2000; Maravall et al., 2004a,b). It also coincides with a developmental shift in AMPAR composition at L4 to L2/3 excitatory synapses. Whisker experience at P12−P14 drives GluA1-containing AMPAR into synapses (Takahashi et al., 2003). Hence, a mechanism that has been shown to drive LTP in vitro (Hayashi et al., 2000) is also invoked by normal whisker experience at L4 to L2/3 synapses.

In contrast to L4 neurons, even removal of all but a single whisker in young adulthood (P28) profoundly alters the receptive fields of L2/3 neurons (Glazewski and Fox, 1996). Two temporally distinct processes underlie plasticity in L2/3 neurons in deprived barrel columns. Depression of responses to the deprived (and briefly regrown) former principal whisker occurs first, within 7 days of whisker removal. Later, potentiation of responses to stimulation of the single remaining whisker is seen (Glazewski and Fox, 1996).

L2/3 neurons integrate input more broadly from neighboring barrel columns. This horizontal synaptic input from L2/3 to L2/3 similarly develops monotonically from P8 to P16 (Bureau et al., 2004) and underlies the surround whisker receptive fields of L2/3 pyramidal neurons (Armstrong-James et al., 1991). It is these horizontal inputs that underlie the potentiation of spared whisker inputs that ultimately drive L2/3 neurons in deprived barrel cortex. This also explains why whisker deprivation paradigms that introduce competition between deprived and spared inputs, such as the chessboard pattern, drive more rapidly plasticity of L2.3 receptive fields (Wallace and Fox, 1999).

Because circuit formation is generally thought to proceed by initial formation of weak connections to many potential targets, followed by strengthening of connections to be retained and elimination of connections that are no longer required (Hooks and Chen, 2006), synapses that weaken as well as strengthen have been studied as part of circuit development. Deprivation studies have shown a role for activity in strengthening feedforward excitation from L4 to L2/3 during initial circuit formation. But there are several components to changes in responsiveness that follow deprivation. A period of susceptibility to long-term depression (LTD) at L4 to L2/3 synapses can be seen in ex vivo recordings. This depression mimics the depression of deprived whisker responses in L2/3 seen in vivo, as in vitro LTD of the L4 to L2/3 connection is occluded following 1−3 weeks of deprivation in young animals (P21−P33) (Allen et al., 2003). Thus, plasticity at this connection temporally follows plasticity at ascending stages of somatosensory input. However, the temporal pattern of the change in responsiveness is likely due to a number of factors. Much like that seen in visual cortex (Kuhlman et al., 2013), there is a rapid reduction in excitatory inputs to FS interneurons, which mediate a substantial component of feedforward inhibition in L2/3 (Li et al., 2014). It is further suggested that rapid changes in FS interneurons occur by a reduction in the intrinsic excitability of these cells (Gainey et al., 2018). The reduction in inhibition initially offsets the reduced sensory-evoked excitation, maintaining cortical firing rates until responsiveness diminishes over a longer period.

7.5.5 Critical periods for inhibition in barrel cortex

Inhibitory synapses in barrel cortex also exhibit critical period plasticity. Inhibitory synapses are present in rodent barrel cortex at least as early as P4 and continue to increase in number and strength across postnatal development until at least P30 (De Felipe et al., 1997). Sensory experience after the second week continues to shape thalamocortical inputs to both inhibitory and excitatory neurons. In particular, thalamocortical synapses onto L4 inhibitory interneurons strengthen by increasing probability of release. This increase in thalamocortical strength can be attenuated by sensory deprivation after P9, a developmental age at which changes in thalamocortical excitation of L4 excitatory cells are no longer evoked (Chittajallu and Isaac, 2010). Functional maturation of synaptic input from interneurons tends to maintain a relatively constant excitation/inhibition ratio (E/I ratio) across most layers after P18, with the most rapid changes occurring from P8 to P18 (Zhang et al., 2011). Maintenance of this balance is hypothesized to prevent runaway excitation and promote stability. Consistent with maintaining this balance, whisker removal during the first two postnatal weeks promotes stronger excitatory responses and weaker inhibitory ones in L4 (Shoykhet et al., 2005).

Overall, the developmental patterns described here reveal sequential developmental periods of susceptibility to activity- and experience-driven plasticity (Fig. 7.9). While gross morphological changes in barrel formation can only be evoked early (before ∼P5), potentiation and weakening of L4 inputs via LTP- and LTD-like mechanisms can occur later (until ∼P8). Functionally, responses in L4 can still be modified by deprivation after P12 (possibly due to intracortical changes). Changes evoked in the intracortical connectivity of the superficial layers of cortex (L2/3) may be evoked even later (P20+). Most importantly, these changes are consistent with a developmental pattern where plasticity in sensory pathways closer to the periphery is downregulated first, whereas hierarchically higher areas may begin synaptogenesis later and retain plasticity until later ages. While adult plasticity is less well studied and more challenging to evoke after the critical period,

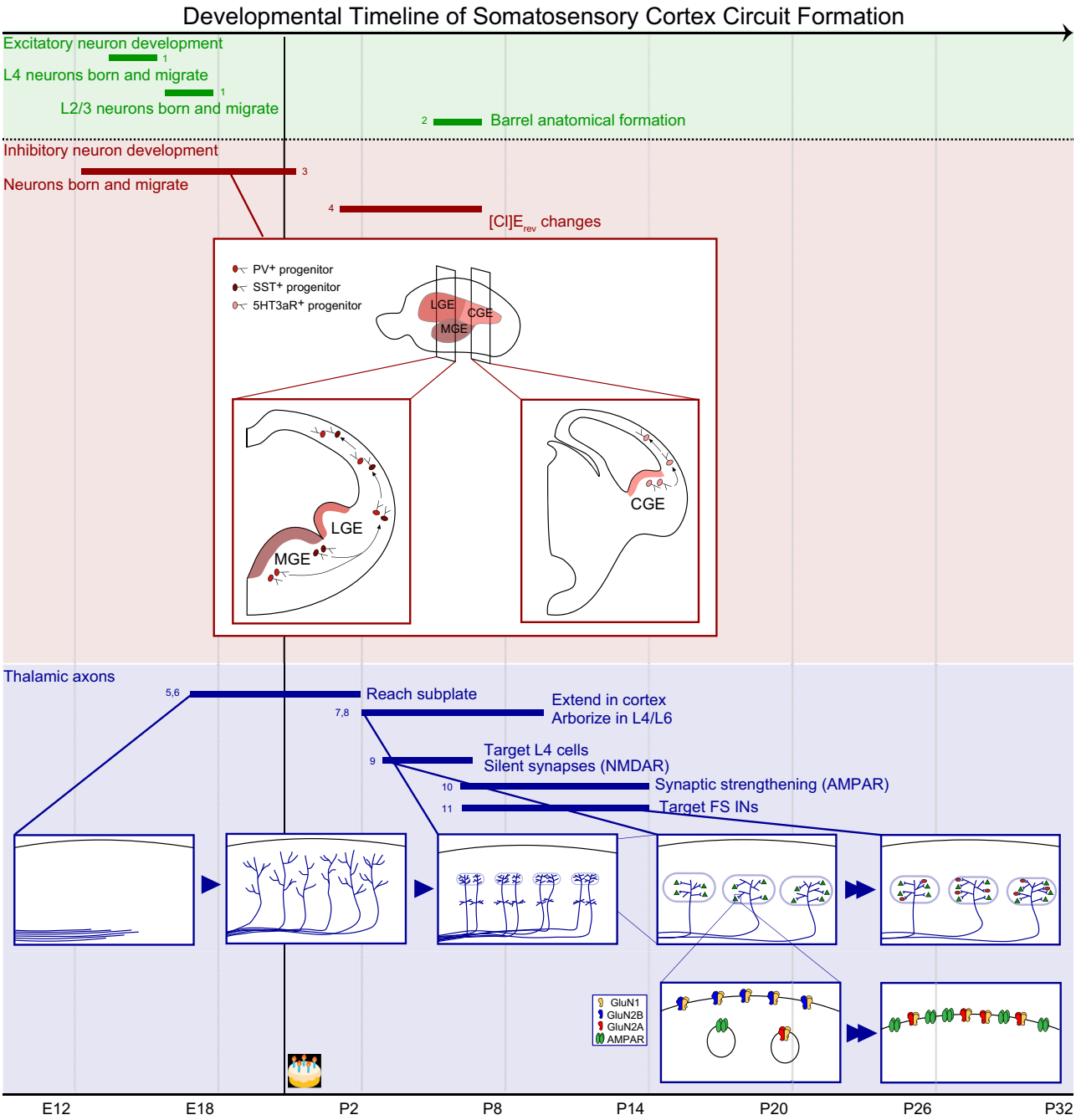

FIGURE 7.9 Developmental timeline of somatosensory cortex circuit formation. Top: Birth and migration of excitatory neurons. Excitatory cells are born in ventricular and subventricular zone. They migrate into the cortex in inside-out pattern. Middle: Birth and migration of inhibitory neurons. Three major types of inhibitory interneurons based on molecular expression are described. PV+ cells are born in ventral medial ganglionic eminence (MGE), whereas SST+ cells are born in dorsal MGE. $5HT_{3A}R$-expressing cells are born in the caudal ganglionic eminence. These inhibitory interneurons migrate into cortex tangentially. After birth, inhibitory input is depolarizing because of higher internal Cl^- concentration. $[Cl^-]i$ gradually decreases during the first postnatal week. Bottom: Thalamic innervation of somatosensory cortex during development. Thalamic afferents (blue) initially target the subplate during embryogenesis and then gradually innervate the cortical layers nonspecifically soon after birth. Thalamic afferents arborize extensively in L4 and between L5B and L6 during the first postnatal week and into the first few days of the second postnatal week. During this period, thalamic axons start to synapse onto L4 excitatory cells (inset, green). Thalamic inputs then excite fast-spiking (PV+) cells (inset, red). Initial synapses include silent synapses, NMDAR-only synapses containing predominantly GluN2B subunits. AMPARs are inserted after the first postnatal week and form functional synapses. A transition from GluN2B to GluN2A subunit composition occurs in NMDAR. *PV*, parvalbumin; *SST*, somatostatin. Footnotes indicate appropriate citations as follows: 1, Rakic (1974) Science 183: 425−427. 2, Rice et al. (1985) J. Comp. Neurol. 236: 477−495. 3, Butt et al. (2005) Neuron 48: 591−604. 4, Owens et al. (1996) J. Neurosci. 16: 6414−23. 5, Rakic (1977) J. Comp. Neurol. 176:23−52. 6, Shatz and Luskin (1986) J. Neurosci. 6: 3655−3668. 7, Catalano et al. (1991) Proc. Natl. Acad. Sci. 88: 2999−3003. 8, Catalano et al. (1996) J. Comp. Neurol. 367: 36−53. 9, Isaac et al. (1997) Neuron 18: 269−280. 10, Malinow and Malenka (2002) Ann. Rev. Neurosci. 25:103−126. 11, Daw et al. (2007) Nat. Neurosci. 10:453−461.

it is worth noting that adult plasticity has a longer time period over which to exert its effect. Plasticity mechanisms include predominantly changes in excitatory and inhibitory synaptic inputs to excitatory neurons, with some contribution of homeostatic mechanisms. Potentially other mechanisms, such as plasticity in inputs to or between inhibitory cells, also contribute and have not yet been fully explored due to technical limitations. Collectively, these mechanisms serve to keep the developing cortex in balance, where neither runaway excitation nor quiescence exclusively reigns.

7.6 Adult plasticity

Critical period closure completely prevents some changes after a certain developmental time point, such as the inability to induce changes to barrel organization by whisker follicle lesion after P5 (Van der Loos and Woolsey, 1973; Woolsey and Wann, 1976). However, many other types of plasticity do not end with critical period closure. Instead, alterations of circuitry require different and often more potent stimuli to evoke changes. Because of the difficulty of inducing complex spatiotemporal patterns of whisker somatosensation, many older studies use sensory manipulations that involve deprivation, which is believed to result in reduced excitatory drive. As a general rule, then, it seems that the magnitude of evoked changes is reduced for the same degree of treatment, such as sensory deprivation. For example, whisker deprivation starting from P12 instead of P0 still evokes increases in L4 excitation and reduction in feedforward inhibition, although the size of the resulting changes is smaller (Shoykhet et al., 2005).

In addition to testing sensory deprivation, studies of corticocortical connectivity can use more precise manipulations, such as testing for the ability to induce spike timing−dependent plasticity in adolescent mice. When spike timing−dependent plasticity of input to L2/3 pyramidal neurons was explored by pairing current injection with principal whisker stimulation, strengthening of synaptic inputs was indeed possible, even at the older age used in this study (>P21) (Gambino and Holtmaat, 2012). Interestingly, such plasticity was not evoked by surround whisker stimulation unless the principal whisker had been trimmed 2−4 days earlier. At similar adolescent ages, whisker trimming starting at P19 greatly reduces local excitatory connectivity within L2/3 of deprived barrel columns (Cheetham et al., 2007). Similar changes can be observed at P30 and correlate with reorganization of the whisker map assessed by functional MRI (Albieri et al., 2015). Translaminar plasticity is also possible in L2/3 synaptic input to L5 pyramidal neurons at such early adult ages. Plasticity varies by L5 pyramidal cell type: Intrinsic bursting L5 cells (also called thick-tufted and likely pyramidal tract-projecting) showed increased L2/3 input following deprivation in contrast to regular spiking L5 neurons (thin-tufted or IT) (Jacob et al., 2012). Collectively, then, these studies have implied that at least some corticocortical connections retain the potential for plasticity longer than connections in ascending pathways. This includes thalamocortical connections, which mature and become less plastic earlier (Feldman and Brecht, 2005).

More recently, this belief about the absence of adult thalamocortical plasticity has been challenged. Adult whisker trimming (using ∼3-month-old animals) resulted in substantial unexpected plasticity in thalamocortical axon arbors in L4. This included a reduction in VPM axon density (Wimmer et al., 2010a) and thalamocortical axon branch length, but a compensatory increase in excitability (Oberlaender et al., 2012). A more complete blockade of sensory activity—by unilateral nerve transection in 4-week-old rats—resulted in prominent changes in cortical responsiveness following 2 weeks of deprivation. MRI imaging shows that deprivation caused a remarkable potentiation of responses to whisker stimulation of the unmanipulated side. This potentiation was due to increase of thalamocortical input to L4 spiny stellate cells (Yu et al., 2012a). Furthermore, the deprived cortex enhanced its responsiveness to ipsilateral (nontransected) whisker stimulation, presumably via strengthening of callosal afferents from contralateral cortex (Yu et al., 2012a). These findings collectively demonstrate that adult circuits retain some capacity for plasticity past adolescence and that such plasticity may help to integrate deprived cortical areas into adjacent neural networks once formerly strong inputs are lost by damage or disease.

7.7 Conclusion

Primary somatosensory cortex has been an outstanding model system for understanding the development and function of cortical circuitry. Its somatotopic organization and well-defined receptive field properties have been used effectively for decades to investigate the role of molecular mechanisms and neural activity in the formation and function of adult circuitry. Because of the large number of cell types in neocortical areas, a comprehensive grasp of the specific circuitry underlying these phenomena has lagged. In this chapter, we offer a current picture of the circuit elements of somatosensory cortex, the specificity of their connections, and changes in their connectivity during development. Although much has become clear in recent decades, considerable efforts are still needed to understand the range of mechanisms by which plasticity might be

implemented in these circuits and the extent to which this plasticity influences specific circuit elements. As new tools are developed for labeling individual circuit components and for probing function and connectivity, it is reasonable to expect more detailed insight into cortical circuit development to emerge.

List of acronyms and abbreviations

ADCY1 adenylate cyclase 1 gene
AMPAR the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, an ionotropic subtype of glutamate receptor and a tetramer whose subunits include GluA1, GluA2, GluA3, and GluA4.
ChR2 channelrhodopsin-2, a light-gated ion channel
FS fast-spiking interneuron, a subtype of interneuron classified by firing pattern
GABA gamma-aminobutyric acid, an inhibitory neurotransmitter
$GABA_AR$ $GABA_A$ receptor
GluA1 a subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, an ionotropic subtype of glutamate receptor and a tetramer whose subunits include GluA1, GluA2, GluA3, and GluA4.
GluA2 a subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, an ionotropic subtype of glutamate receptor and a tetramer whose subunits include GluA1, GluA2, GluA3, and GluA4.
GluA3 a subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, an ionotropic subtype of glutamate receptor and a tetramer whose subunits include GluA1, GluA2, GluA3, and GluA4.
GluA4 a subunit of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, an ionotropic subtype of glutamate receptor and a tetramer whose subunits include GluA1, GluA2, GluA3, and GluA4.
GluN1 a subunit of the *N*-methyl-D-aspartate receptor subtype of glutamate receptors, a tetramer that includes obligatory subunit GluN1 and subunits GluN2A and GluN2B
GluN2A a subunit of the *N*-methyl-D-aspartate receptor subtype of glutamate receptors, a tetramer that includes obligatory subunit GluN1 and subunits GluN2A and GluN2B
GluN2B a subunit of the *N*-methyl-D-aspartate receptor subtype of glutamate receptors, a tetramer that includes obligatory subunit GluN1 and subunits GluN2A and GluN2B
IT type intratelencephalic type (IT type), a subset of L5 cortical neurons
L1 cortical layer 1
L2 cortical layer 2
L2/3 cortical layers 2 and 3
L3 cortical layer 3
L4 cortical layer 4
L5 cortical layer 5 (5A and 5B)
L5A cortical layer 5A
L5B cortical layer 5B
L6 cortical layer 6
LTP long-term potentiation
LTS low-threshold spiking interneuron, a subtype of interneuron classified by firing pattern
M1 primary motor cortex
mGluR5 metabotropic glutamate receptor 5
NGFC neurogliaform cells, a subtype of interneuron classified by morphology
NMDAR The *N*-methyl-D-aspartate receptor subtype of glutamate receptors, a tetramer that includes obligatory subunit GluN1 and subunits GluN2A and GluN2B
Ntsr1_GN220 a Cre-driver mouse line that expresses Cre in L6 corticothalamic neurons
PI3K phosphoinositide 3-kinase, an intracellular signaling molecule
PKA protein kinase A, a cAMP-dependent protein kinase
PLC-β1 phospholipase C-β1
POm medial subdivision of posterior nucleus of thalamus
PT type pyramidal tract type (PT type), a subset of L5 cortical neurons
PV parvalbumin, a marker for a subtype of inhibitory interneuron
RAS/MAPK a signaling pathway involving Ras, a small GTPase and mitogen-activated protein kinase
RIM1 regulating synaptic membrane exocytosis protein 1, a protein for synaptic release
RIM2 regulating synaptic membrane exocytosis protein 2, a protein for synaptic release
S1 primary somatosensory cortex (also called barrel cortex)
S2 secondary somatosensory cortex
SBCs single bouquet cells, a subtype of interneuron classified by morphology
SST somatostatin, a marker for a subtype of inhibitory interneuron

SynGAP synaptic Ras GTPase-activating protein 1, an activator of GTPases in intracellular signaling
VIP vasoactive intestinal peptide, a marker for a subtype of inhibitory interneuron
VPM ventroposteromedial nucleus of thalamus
5-HT$_{3A}$R The 5-HT$_{3A}$ receptor, a serotonin receptor subtype that marks a subtype of inhibitory interneurons

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