How the Barrel Cortex Became a Working Model for Developmental Plasticity: A Historical Perspective

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Viewpoints

How the Barrel Cortex Became a Working Model for Developmental Plasticity: A Historical Perspective

Reha S. Erzurumlu[1] and Patricia Gaspar[2]

[1]Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, Maryland 21201, and [2]Institut National de la Santé et de la Recherche Médicale, Paris Brain Institute, Sorbonne Universités, Paris, France 75013

For half a century now, the barrel cortex of common laboratory rodents has been an exceptionally useful model for studying the formation of topographically organized maps, neural patterning, and plasticity, both in development and in maturity. We present a historical perspective on how barrels were discovered, and how thereafter, they became a workhorse for developmental neuroscientists and for studies on brain plasticity and activity-dependent modeling of brain circuits. What is particularly remarkable about this sensory system is a cellular patterning that is induced by signals derived from the sensory receptors surrounding the snout whiskers and transmitted centrally to the brainstem (barrelettes), the thalamus (barreloids), and the neocortex (barrels). Injury to the sensory receptors shortly after birth leads to predictable pattern alterations at all levels of the system. Mouse genetics have increased our understanding of how barrels are constructed and revealed the interplay of the molecular programs that direct axon growth and cell specification, with activity-dependent mechanisms. There is an ever-rising interest in this sensory system as a neurobiological model to study development of somatotopy, patterning, and plasticity at both the morphologic and physiological levels. This article is part of a group of articles commemorating the 50th anniversary of the Society for Neuroscience.

Milestones in barrel cortex development and plasticity: discovery and coining the term "barrels"

The Society for Neuroscience was founded by Ralph Waldo Gerard in 1969, and the first meeting of the Society for Neuroscience gathered in Washington, DC in 1971. Coincidentally, the term "barrels" was coined in 1969, not far from Washington, DC by Thomas Woolsey, a medical student under the supervision of Hendrik Van der Loos at the Johns Hopkins University in Baltimore. Early cytoarchitectonic studies had already noted unusual clusters of neurons in layer 4 in the lateral cortex of rodents (de Nó, 1922; Rose, 1929), but the functional correlate of this anatomic organization was unclear and was wrongly attributed to the auditory cortex. It was Thomas Woolsey who made the observation that the whiskers on the snout of mice are represented by a patterned array of cylindrical neural aggregates in the somatosensory cortex. Using Nissl and Golgi staining, Woolsey and Van der Loos described the clustering of layer 4 neurons around a central, cell-sparse region (named the hollow) that was most clearly visible in thick brain sections cut tangential to the cortical surface. They further demonstrated a remarkable, one-to-one correspondence between the layout of the barrels with those of the large mystacial vibrissae in the whisker pad. This landmark paper was published in 1970 in the then leading neuroscience journal, *Brain Research*. To give a sense of the excitement of this discovery, we include here excerpts from Tom Woolsey's (2016) review of the Woolsey and Van der Loos (1970) paper:

> "In the summer of 1965, before entry in medical school at The Johns Hopkins, I worked in the Laboratory of Neurophysiology mapping sensory evoked potentials in the cerebral cortex of mice. This was a suggestion (assignment?) from my father [Clinton Woolsey] who had published studies of cortical evoked potential maps of rats in the late '40s (Woolsey, 1952)... I noticed that, unlike the Nissl stained sections of the human brains... the sections of mouse brains had odd patterns of layer IV neurons in the somatosensory cortex. The region with patterns corresponded directly with the region that responded to stimulation of the facial whiskers- vibrissae- on the contralateral face.... I published an article on cortical localization of sensory functions in mouse (Woolsey, 1967).... I approached a then Assistant Professor of Anatomy who had taught neuroanatomy to us in our first year... Hendrik Van der Loos, MD, PhD (Molliver et al., 1994). From his lectures we learned that he had developed a staining method combining Golgi and Nissl staining. I thought this would be excellent for understanding organization of cell clusters in the 'whisker' cortex... In the Van der Loos laboratory, I learned and used the technique for embedding tissues in celloidin for slicing thicker sections on sliding microtomes. This was an obvious advantage for accurately slicing mouse brains tangential to the right brain surface location to visualize the cytoarchitecture of the whisker cortex in layer IV.

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Correspondence should be addressed to Reha S. Erzurumlu at rerzurumlu@som.umaryland.edu.

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> The first Nissl stained slides showed the answer! Rings of neurons arranged in 5 rows mirroring the pattern of whiskers on the contralateral face and in layer IV of the cortex activated by whisker stimulation were obvious. In three dimensions they resembled cylinders tapered at the junctions with layers III above and V below. I named these structures barrels. The larger whiskers matched what I termed the posterior medial barrel sub-field (PMBSF) of the mouse somatosensory cortex (SmI)... I put together the collages of photomicrographs and images of the tangential sections... In the spring of 1969, I wrote the manuscript and completed the graphics. In discussion with Van der Loos, he asked why I had added his name as author.... I pointed out the science had been done largely in his laboratory and this was appropriate... We submitted the article to *Brain Research* in the summer of 1969.... We both were astounded to receive a letter from Professor Konrad Akert, the founder and chief editor of *Brain Research*, dated 2 weeks after the manuscript arrived in Zurich,... accepting the paper without any changes."

Following this pioneer paper, Van der Loos and Woolsey (1973), tested the hypothesis that signals derived from the whiskers informed barrel cortex development. The first landmark experiment was a cauterization of whisker rows in newborn mice followed by anatomic investigation of the barrel field layout several weeks later. The striking result was that lesions performed during the first few days of life prevented the formation of the corresponding barrel structures. Frank Rice, a graduate student of Van der Loos at the time, remembers this period as follows (personal communication):

> "I began my PhD studies in the Department of Anatomy at Johns Hopkins Medical School in 1969 where Hendrik [Van der Loos] was on the faculty I think as an Associate Professor. I remember his promotion to Professor while I was there.... I fell in love with the Neuroanatomy Course taught almost entirely by Hendrik, which began in December 1969... we hit it off very well. I believe Tom [Woolsey] was in his last year of med school in 69–70... That was right at the time of the first publication and when the first whisker cauterization study was in progress.... Tom's father earned renown for the physiological mapping showing the detailed fundamental principle of somatotopic organization of the cortex in several species.... So, Tom followed in his father's footsteps. He mapped the mouse cortex in the physiology department as Summer research project. I am pretty sure that it was Tom who knew of the cytoarchtectonic studies of Rose from the 1920s... deduced from sensory deficits in stroke patients. Tom recognized that those structures were physiologically located in somatosensory cortex. So, he worked with Hendrik to learn the celloidin technique where they gradually changed the cutting angle to being parallel to the cortical surfaces where the 'barrel' pattern representing the whiskers became evident. So that was pretty much Tom's work. Hendrik came up with the whisker cauterization study, which was entirely done by him and his wife Nolette. So, I was there when the sections were first coming out with the excitement of the missing rows of barrels, which led to the question of whether the barrels developed before or after the neonatal cauterizations, which became my thesis project."

The above-referred studies started the "whisker-barrel" research. Shortly after these publications, Woolsey and Van der Loos parted ways and pursued productive "barrel" research in their own respective laboratories. They made many other important contributions to the field, including naming the whisker-related cellular aggregates in the thalamus "barreloids" (Van der Loos, 1976) and those in the brainstem "barrelettes" (Ma and Woolsey, 1984).

How the barrel cortex became a developmental model

As a PhD student of Hendrik Van der Loos, Frank Rice followed him to Lausanne to finish his dissertation work. There, they set up an entire laboratory devoted to the understanding of barrel development, including studies of how genetic variations of the whisker implantation or function affected barrel organization. Using simple histologic stains (Nissl), Rice and Van der Loos showed that "the onset of barrel formation coincides with the moment after which injury to the pertinent somatosensory periphery no longer causes profound alterations in barrel morphology" (Rice and Van der Loos, 1977). Using comparative "evo-devo" strategies, they also showed that barrel-like somatosensory cortical patterning is present in most rodents that whisk (hamster, mouse, rat, and gerbil) while it is sparse or absent in species that minimally or never whisk (guinea pig, rabbit, and cat) (Rice, 1985a,b; Rice et al., 1985). These experiments indicated that the peripheral sensory receptors and their function were important drivers of anatomic organization, inspiring further studies on how the innervation to vibrissal follicle-sinus complexes develops during embryonic life (Fig. 1) (Rice et al., 1997; Cronk et al., 2002; Ebara et al., 2002).

Not just neurons, axon terminals too replicate the whisker patterns

Around the same time of the initial barrel papers, Herbert Killackey, a postdoctoral fellow with Ford Ebner, was studying thalamocortical (TC) projections in the opossum (Killackey and Ebner, 1972, 1973). Enthused by the mouse barrel cortex, he used the method of the time, silver impregnation of degenerating axons, and demonstrated a whisker-related discontinuous pattern of TC axons in the SI cortex of rats (Killackey, 1973). Killackey started the third pioneering laboratory in barrel research as a new Assistant Professor at the University of California, Irvine (Killackey and Leshin, 1975). One of us (Erzurumlu) had doctoral training (1977–1981) with Herb Killackey, and worked on the connections of the brainstem trigeminal nuclei and topographic order in the trigeminal nerve and ganglion (Erzurumlu and Killackey, 1979, 1980, 1982a,b, 1983).

Emergence of new markers for barrel development

Before immunocytochemistry (or genetic labeling) became prevalent, enzymatic histochemistry provided useful tools to visualize sensory maps, often with primary studies in the visual system (which was the hot topic in neuroscience at the time) and follow-up studies in the barrel cortex. In one such line of work, Margaret Wong-Riley showed that mitochondrial enzyme, cytochrome oxidase (CO) histochemistry could be used reliably to visualize patterns along the visual pathway and following sensory deprivation (Wong-Riley et al., 1978; Wong-Riley, 1979). This

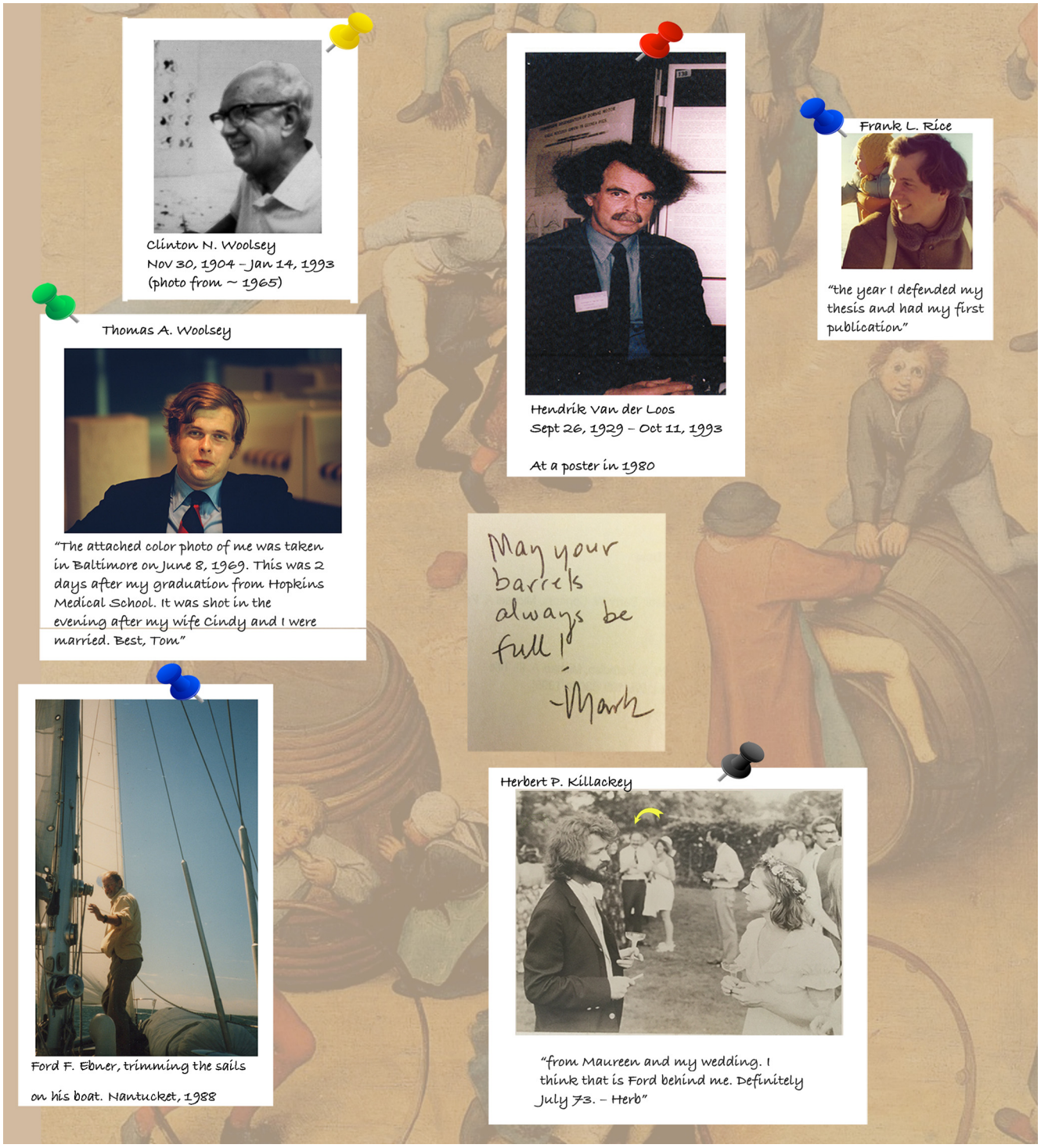

Figure 1. Barrel research pioneers. Photographs of Tom Woolsey's father Clinton Woolsey taken around 1965 and Tom Woolsey, right after the first barrels paper was submitted, but before its acceptance, from a happy time, the evening of his wedding. Hendrik Van der Loos, at a poster in 1980. Frank Rice in Switzerland, the year he defended his PhD thesis. Herb Killackey, at his wedding in Providence, RI, in 1973, with Ford Ebner in the background. Bottom left, Ford Ebner in 1988, preparing to sail to "the ocean of barrel cortex plasticity" in the years to come (photograph by R.S.E.). Autograph in the middle of the figure is that of Mark Bear (a former student of F. Ebner) from 1995, when he was visiting R.S.E. at Louisiana State University Health Sciences Center in New Orleans. We are grateful to Tom Woolsey, Frank Rice, and Herb Killackey for providing the original photographs of the discoverers and pioneers, just when all was happening and they were enjoying happy times in their lives.

suggested that the same histochemical staining could be used for visualization of the barrel patterns in normal and neonatally vibrissa-removed mice (Wong-Riley and Welt, 1980). Succinic dehydrogenase, another mitochondrial marker, was found by Gary Belford (then a graduate student of Herb Killackey) to be another useful marker of the barrel cortex. The prevailing thought then was that cortical "activity levels of SDH or CO closely corresponded to the patterns of thalamocortical afferent terminals" (Killackey and Belford, 1979), but, although enriched in axon terminals, mitochondrial enzymes label both the presynaptic and

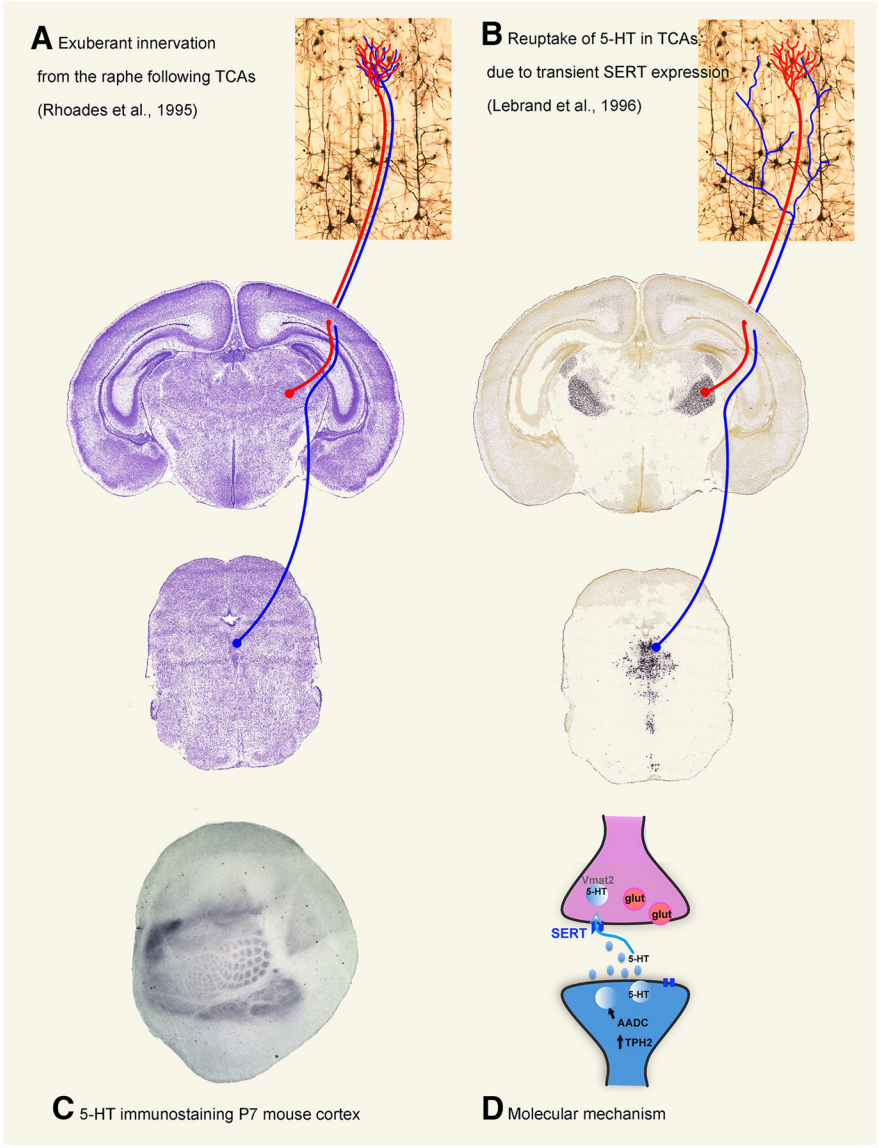

Figure 2. In a landmark paper published in 1987, D'Amato et al. (1987) reported the presence of a transient, dense, serotonergic innervation in all primary sensory areas of cortex, including the barrel cortex (***A***). This is visible on tangential sections of cortex at P7 (***C***) and was interpreted as an exuberant serotonergic innervation from the raphe, which followed sensory TC axons and was subsequently pruned (***A***). Later observations (Lebrand et al., 1996) demonstrated that serotonin (5-HT) is indeed captured by the developing sensory TC axons because of the expression of the serotonin transporter (SERT/*Slc6a3*) and the vesicular monoamine transporter (VMAT2/*Slc18a4*) in the sensory thalamic neurons. The expression of these 2 genes starts in embryonic life (EXIV) and ends during the second postnatal week (P10) in mice. ***B***, Thus, raphe neurons are not exuberant, but 5-HT staining reflects transient neurotransmitter properties of glutamatergic thalamic sensory neurons. As schematized in ***D***, raphe brainstem neurons (blue) synthesize 5-HT via 2 enzymes, tryptophan hydroxylase (TPH2) and amino acid decarboxylase (AADC). Axon terminals of raphe neurons release 5-HT in the developing brain/cortex, which is captured from the extracellular space by glutamatergic (glut) neurons (pink) that express the high-affinity membrane transporter, SERT. In the cytoplasm, 5-HT is then concentrated into synaptic vesicles by VMAT2, where it is protected from monoamine-degrading enzymes, in particular monoamine oxidase (MAOs). Nissl and SERT ISH images are from the Allen Brain Atlas: Mouse Brain (Slc4-79591679).

postsynaptic elements (Kageyama and Wong-Riley, 1982). Because of the simplicity of CO staining and the clear delimitation of barrel topology it provided in cortical flat mounts, CO histochemistry took over and has been used ever since to visualize barrels.

Serotonin immunocytochemistry (Fig. 2*A*), AChE histochemistry (Kristt, 1979; Schlaggar and O'Leary, 1994), and labeling of extracellular matrix molecules started to be investigated at that time because of their precocious appearance and the observation that they clearly labeled the barrels at early stages (Cooper and Steindler, 1986; D'Amato et al., 1987; Steindler et al., 1989; Rhoades et al., 1990). Serotonin labeling in the barrel cortex was initially interpreted as a transient overgrowth of raphe axons into the somatosensory cortex (D'Amato et al., 1987; Rhoades et al., 1990) (Fig. 2*A*). However, later studies showed that there is no exuberant innervation from the raphe but that serotonin is indeed taken up in TC terminals (from E15 to P10) through transient expression of the serotonin transporter (5-HTT, SERT, *Slc6a4*) and the vesicular monoamine transporters (VMAT2, *Slc18a2*) in the developing thalamus (Lebrand et al., 1996, 1998) (Fig. 2*B*,*D*). Serotonin or SERT immunocytochemistry has since then been used as markers of the developing TC axons. More recently, SERT expression in the developing TC axons has been used to create genetically modified mice in which the SERT promoter drives GFP expression (Moreno-Juan et al., 2017; Mizuno et al., 2018).

Other useful markers of barrels have emerged since. In particular, vesicular glutamate transporter 2 (VGluT2), one of the two isoforms of the vesicular glutamate transporter, was found to be expressed selectively in the TC afferents (Nahmani and Erisir, 2005), and VGluT2 immunocytochemistry rapidly became a standard for analyzing barrel cortex (Fig. 3) (Liguz-Lecznar and Skangiel-Kramska, 2007; Nakamura et al., 2007).

TC axons as major players of barrel development

In the discussions centered around what initiated the barrel patterns in the cortex, a main issue in the early days was the difficulty of tracing axons in developing brains. An important turning point was brought about in 1987, by the introduction of the lipophilic carbocyanine dyes that could be used as neuronal tracers in fixed tissues (Godement et al., 1987). Carbocyanine dye labeling and single-axon reconstruction along the barrel system revealed that TC axons begin invading the cortical plate at the time of birth in both mice and rats (Erzurumlu and Jhaveri, 1990; Senft and Woolsey, 1991). This allowed Erzurumlu and Jhaveri (1990, 1992) to document the time course of TC axon development in the parietal cortex. Simultaneous labeling of TC axons and raphe cortical projections with different colored carbocyanine dyes in the same brain (Erzurumlu and Jhaveri, 1992),

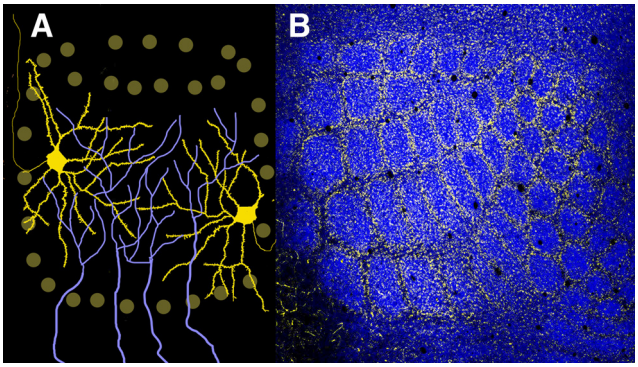

Figure 3. ***A***, What is in a barrel? Glutamatergic spiny stellate and star pyramidal cells (yellow) of layer 4 aggregate along the walls of a barrel in the mouse SI cortex. Their dendrites orient toward the barrel hollows that are filled with the terminal arbors (blue) of TC axons from the whisker representation (barreloid) zone of the VPM. Axons of barrel cells project mostly to the supragranular (2/3) layers. ***B***, Photomicrograph of a PND7 mouse barrel cortex immunostained for VGluT2 (blue), a marker for TC axons, and NeuN (yellow) to mark the nuclear architecture of layer 4.

or comparisons of carbocyanine dye labeling of thalamic afferents and serotonin immunocytochemistry in opposite hemispheres of the same brain (Blue et al., 1991), proved that TC axons are the first pattern forming elements, while clustering of neurons in layer 4 occur 1 d later.

How mouse genetics opened a window to the mechanisms underlying barrel formation

The use of mouse genetics to study barrel cortex development was started in the1980s by Hendrik Van der Loos and Egbert Welker in Lausanne. This involved labor-intensive screening of mice with spontaneous mutations that led to abnormal number and patterns of vibrissae and/or barrel fields. By the 1980s, it was well established that the sensory periphery plays an instructive role in barrel patterning; damage to whisker follicles or the presence of supernumerary vibrissae on the snout (Van der Loos et al., 1986; Welker and Van der Loos, 1986) had predictable consequences in brain regions representing the vibrissae.

A surprising observation was that of a spontaneous mutation in which no barrels formed in the cortex despite a normal whisker pad and normal barrel patterning in the brainstem and thalamus (Welker et al., 1996). In these mice, TC axons form broader terminations, barrels do not develop, and whisker receptive fields of cortical cells are broader (Welker et al., 1996; Gheorghita et al., 2006). This mutation was identified, a few years later (Abdel-Majid et al., 1998), as a spontaneous disruption of the adenylate cyclase 1 gene (*Ac1)*.

At exactly the same time as discovery of the "barrelless" mutation, another mouse mutant with a similar phenotype was discovered by one of us (P.G.) while conducting research on the developmental role of serotonin (5-HT). Mouse mutants with excess 5-HT, resulting from disruption of the monoamine oxidase A (*Maoa*) gene, had no barrels, but normal patterning in the thalamus and the brainstem. These effects were reversed (barrels formed) by reducing 5-HT levels and were replicated by pharmacological blockade of MAOA during the critical period. Previously, it was reported that 5-HT_{1B} receptors are also transiently expressed in the developing thalamus (Bennett-Clarke et al., 1993), and 5-HT has a role in inhibiting glutamate release (Rhoades et al., 1994). The Gaspar group took this a couple steps further; with genetic tools, they showed that lack of 5-HT_{1B} rescued the phenotype of *Maoa* KO mice (Salichon et al., 2001). Whole-cell patch-clamp recordings of layer 4 neurons showed a strong presynaptic inhibitory effect of 5-HT_{1B} signaling on TC axons (Laurent et al., 2002). Collectively, these findings demonstrated that TC axons autoregulate their glutamate release via extracellular 5-HT binding to their 5-HT_{1B} receptors. Although the phenotypes of *Maoa* and *Ac1* KO are very similar, it remains unclear whether they share similar mechanisms.

Other genetically modified mouse models are discussed in the following sections.

Development of TC axons: first encounters guide topography

Along the trigeminal pathway, axon navigation and pattern formation do not follow a sequential order from the periphery to the cortex. Rather, they happen concurrently (Iwasato and Erzurumlu, 2018). In mice, TC axons from the ventroposteromedial nucleus (VPM) are already at the diencephalon-telencephalon border by embryonic day (E) 12.5 (López-Bendito et al., 2006; Antón-Bolaños et al., 2018), well before the trigeminothalamic afferents reach the VPM around E15.5 (Kivrak and Erzurumlu, 2013).

TC axons are preordered and maintain near-neighbor relationships as they navigate through the subpallium (Molnár et al., 2012). Perturbation of subpallial development by conditional inactivation of the transcription factor Ebf1 leads to misrouting of the TC axons and disruption of their topography and patterning in the barrel cortex (Lokmane et al., 2013). The role of axon fasciculation in establishing topographic organization in the barrel map is nicely illustrated in mouse mutants in which the trigeminothalamic axons project bilaterally (Renier et al., 2017) and form distinct ipsilateral and contralateral domains in the VPM. In these mice, TC axons segregate into two independent barrel cortices that lie side by side, suggesting that axons traveling together prefer remaining together rather than following topographic rules (Renier et al., 2017; Gaspar and Renier, 2018).

TC axons arrive below the cortical plate by E13.5, before the differentiation of the prospective barrel site in layer 4 (Erzurumlu and Jhaveri, 1990; Senft and Woolsey, 1991; Catalano et al., 1996). They transiently interact with subplate cells, forming functional synapses (for review, see Kanold and Luhmann, 2010). Early ablation of subplate neurons during embryonic life prevents thalamic axons from penetrating into the cortex (for review, see Hoerder-Suabedissen and Molnár, 2015). Processes of the subplate cells continue to interact with TC axons well into the early postnatal period during whisker-related patterning of TC axons (Piñon et al., 2009), and immunotoxic lesions of the subplate disrupt barrel formation (Tolner et al., 2012).

Shaping TC axons into barrel clusters

Whether TC axons are already topographically organized in barrel domains when they reach the cortex or whether periphery-related organization emerges later has been debated. In the mouse brain, Senft and Woolsey (1991) described TC axon terminals as "whisker-related Gaussians" that initially overlap but later (after postnatal day [PND] 4) segregate into whisker-related patches as appropriate collateral branches are elaborated and inappropriate ones pruned. In the rat, Catalano et al. (1996) described a simpler development, in which single axonal arbors had fewer branches initially and became elaborated without exceeding barrel boundaries. A later carbocyanine-dye-labeling and single-axon-reconstruction study in the mouse (Agmon et

al., 1993) documented that TC axons course through layers 6 and 5 with little or no branching on PND0, develop lower-tier branches at the border of layers 5 and 6 by PND2, and begin elaborating patchy dense clusters in layer 4 by PND4. The authors concluded that TC terminals in layer 4 projected from the deep tier and "do not develop from an initially profuse arborization pattern through pruning of inappropriate branches." The P.G. and R.S.E. laboratories conducted single-TC axon reconstruction studies in (C3H and C57Bl/6) mice and compared them with those from *Maoa* and *NR1* (*Grin1*) KO mice, respectively (Rebsam et al., 2002; Lee et al., 2005) and showed a somewhat different picture, with earlier branching in layer 4 and lack of prepatterning in deep layers. These results paved the way for future studies with KO models to sort out the role of presynaptic versus postsynaptic elements in pattern formation.

Presynaptic and postsynaptic communication in barrel formation

Mouse models with region-specific gene KO have been powerful instruments in dissecting the roles of presynaptic and postsynaptic elements of TC circuits in pattern formation. This approach became feasible with the introduction of site-specific recombination in mice using the Cre-lox recombination (Sauer and Henderson, 1988; Tsien et al., 1996). The first of these mouse lines involved KO of *Grin1* (NMDA receptor subunit 1) in excitatory cortical neurons (Iwasato et al., 2000). In these mice, layer 4 neurons failed to orient their dendritic trees and TC terminals developed extensive arbors that did not focalize in layer 4 (Iwasato et al., 2000; Datwani et al., 2002b; Lee et al., 2005). A similar glutamatergic transmission defect was reported for cortex-specific metabotropic glutamate receptor *mGluR5* KO mice (Ballester-Rosado et al., 2010).

Obviously, the main questions in site-specific gene deletions were whether TC patterning and dendritic orientation of barrel cells depended on each other. These questions were addressed in mosaic cortical-gene-deletion models, in which only a subset of layer 4 neurons lost *Grin1*, *Grin2*, or *mGluR5*. These studies revealed that lack of one of these glutamate receptors alters dendrite organization of layer 4 neurons (Espinosa et al., 2009; Ballester-Rosado et al., 2010; Mizuno et al., 2014).

Genetic ablation of thalamic *Grin1* or *Ac1*, an enzyme that increases cyclic AMP in response to calcium influx, led to absence of barreloids in the thalamus and subsequently barrels in the cortex (Iwasato et al., 2008; Arakawa et al., 2014b; Suzuki et al., 2015). Despite the absence of neuronal aggregate patterns, in both instances, some whisker-related patterning of TC could be seen. Along similar lines, thalamus-specific deletion of RIM1 and RIM2 proteins, which control synaptic vesicle fusion and neurotransmitter release, yielded a phenotype with absence of barrels as cellular aggregates but presence of distinct TC terminal patterns in the whisker representation area (Narboux-Nême et al., 2012). Thus, it appears that, when thalamic cells lose NMDAR or AC1 function or have significantly reduced presynaptic glutamate release from their terminals (thalamic *Rim1/Rim2* double KO), the TC axons can still manage to form faint or partial whisker-related patterns in the barrel cortex. Nonetheless, with complete deletion of glutamatergic transmission in the VPM, in *VGluT1-VGluT2* double KO, TC axons do not form patterns in the cortex (Li et al., 2013).

Recently, evaluation of barrel phenotype in staggerer mice (with a mutation of the gene encoding the retinoic acid-related orphan receptor α [RORα]) revealed disruption of patterns both in the thalamus and cortex. Conditional *Rorα* deletion in the thalamus or cortex showed that RORα is cell-autonomously required in the thalamus for clustering of TC axons and dendritic maturation of layer 4 neurons in the barrel cortex (Vitalis et al., 2018). In an earlier study, Matsui et al. (2013) found that dendritic orientation of barrel cells is controlled by the BTB/POZ domain-containing 3 (BTBD3) transcription factor, and when ectopically expressed in the ferret visual cortex, BTBD3 directs dendrites of cortical cells toward active axon terminals. Interestingly, BTBD3 appears to be controlled by the transcription factor Lhx2 discussed above (Wang et al., 2017).

Despite all these elaborate genetic studies, almost half a century after the first description of patterning of whisker-related TC terminals in the rodent barrel cortex (Killackey, 1973; Killackey and Leshin, 1975), we still do not know the exact mechanisms by which the TC axon terminals form clusters, replicating the distribution of whisker follicles, three synapses away from the periphery. Nonetheless, the emerging picture is that whisker-related TC axons begin focalizing their terminals in an activity-dependent manner. During this process, they regulate their own glutamate secretion through 5HT-1B receptors binding extracellular serotonin delivered to the cortex via raphe terminals (Bennett-Clarke et al., 1993, 1996, 1997; Lieske et al., 1999; Young-Davies et al., 2000; Salichon et al., 2001). Focalized activity of TC axon terminal patches is detected by the postsynaptic spiny stellate and star pyramid cells (barrel cells) in an NMDA receptor-dependent manner, and BTBD3 directs orientation of barrel cell dendrites toward the TC terminal patches, subsequently forming the barrel rings. *In vivo* time-lapse imaging of labeled TC axons and individual barrel cell dendrites revealed dynamic orientation of the dendrites toward focalized TC patches; and in NMDAR-deficient barrel cells, the motility increased and orientation bias failed to develop (Mizuno et al., 2014; Nakazawa et al., 2018).

Curiously, the barrels in the rat cortex resemble those of the mouse cortex with cell-sparse centers until PND20, and then barrel centers become uniformly cell-dense (Rice, 1985a), despite the patterning of TC axons.

Specification of sensory cortices: intrinsic versus extrinsic determinants

The development of TC axons and their major impact on the formation of barrels became a central model in the broader debate on the mechanisms underlying specification of cerebral cortical areas (Rakic, 1988; O'Leary, 1989). Two main hypotheses were discussed at the time. One hypothesis was that the neocortex is a "tabula rasa" on which TC axons impress their characteristics. Strong support for this hypothesis was provided by the whisker lesion studies showing that sensory input was crucial to imprint barrel patterns and by grafting experiments showing that pieces of visual cortex transplanted into the somatosensory cortex could develop TC axon patches (Schlaggar and O'Leary, 1991). Furthermore, when visual or auditory inputs were rerouted to the somatosensory thalamus, the somatosensory cortex would become responsive to visual or auditory cues (Gao and Pallas, 1999; Frost et al., 2000; Sharma et al., 2000).

An alternative hypothesis held that there are intrinsic cortical cues (proto map) that direct TC axon connectivity. In support of this hypothesis, Rakic et al. (1991) provided evidence that reducing the population of selected thalamic fibers projecting into the primary visual cortex of monkeys during midgestation induced the formation of a novel cytoarchitectonic area, which they called

area X. Topographic projections from the visual thalamus to the primary visual cortex of congenitally anophthalmic mice (Kaiserman-Abramof et al., 1980) strengthened this hypothesis. Several years later, more evidence came from the barrel cortex. This was based on the finding of a transgene (*H-2Z1*), of unknown function, but whose expression was found to be intrinsic to layer 4 of the somatosensory cortex. Expression of *H-2Z1* was found to be independent from sensory inputs, and to persist in heterotopic grafts and in cultured explants (Cohen-Tannoudji et al., 1994; Gitton et al., 1999). The balance of evidence shifted further toward the "proto map" hypothesis with the seminal paper by Fukuchi-Shimogori and Grove (2001), showing that cortically secreted signaling molecule FGF8 determines the sites of different sensory areas.

We now know that the neocortex is not a "tabula rasa"; instead, spatiotemporal regulation of morphogens, some of which are induced by sensory afferents, regulates the areal parcellation (Frangeul et al., 2016). Indeed, a variety of intrinsic cortical signaling molecules involved in positioning and patterning barrel maps have been discovered (Zembrzycki et al., 2013, 2015; Stocker and O'Leary, 2016; for review, see Simi and Studer, 2018), and developmental studies using the barrel cortex as a model have revealed many important mechanisms underlying specification and arealization of the mammalian cerebral cortex.

Molecular signals involved in cortical specification

Cortical cues that are produced very early in development shape the regional identity and define the position and dimensions of the prospective somatosensory cortex (and other primary sensory cortices). These signals will, in turn, attract specifically VPM TC axons. Along the rostrocaudal and mediolateral dimensions of the telencephalic vesicles that give rise to the neocortex, diffusible morphogens and signaling molecules, such as Fgf8, Pax6, Emx2, Sp8, and Couptf1, establish a fate map area in the ventricular zone. This fate map is later transferred to the cortical plate and defines the location and boundaries of the primary sensory, motor, and association areas (Greig et al., 2013). The development of *in utero* electroporation techniques permitted ectopic manipulation of morphogen expression in the embryonic cortex, and the resulting phenotypes were quite amazing, leading to altered positioning of the barrel cortex along the rostrocaudal dimension of the brain hemisphere. Most remarkably, creating two sources of fibroblast growth factor (fgf8) on either pole of the telencephalic vesicle led to duplicate barrel fields (Fukuchi-Shimogori and Grove, 2001) and expression in multiple points led to multiple fractured barrel maps (Assimacopoulos et al., 2012). Similarly, manipulation of *Pax6*, *Emx1*, or *Lhx2* in early embryos led to differential expansion or contraction of primary sensory cortical areas (Zembrzycki et al., 2013, 2015; Stocker and O'Leary, 2016). Interestingly, the early sensory TC inputs to the cortex contribute to the expression of region-specific transcriptomes, as removal of these inputs leads to a respecification of the primary somatosensory area into associative or secondary sensory area (Vue et al., 2013; Pouchelon et al., 2014; Frangeul et al., 2016).

At somewhat later stages in development, when corticogenesis is underway, other molecular cues are important to guide TC axons to their proper cellular targets (López-Bendito et al., 2006). Cortical principal (glutamatergic) neurons are highly diverse in terms of connectivity and physiology. Although cortical identity was initially defined by laminar position, it is increasingly becoming clear that identity is defined by birth order and by molecular profile, which in turn determines a preferred connectivity (Greig et al., 2013; Govidan and Jabaudon, 2017). TC axons from the VPM preferentially target layer 4 spiny stellate neurons (Simi and Studer, 2018). Changes in the laminar position of layer 4 neurons as a result of migration defects does not alter this preferential targeting. For example, in the *reeler* mouse, different types of cortical neurons are intermingled in a chaotic fashion because the normal inside out migration of cortical neurons is disturbed. Despite the shuffling of cortical neurons, TC axons recognize stellate neurons, target them, and form rudimentary barrel-like patterns. More importantly, whisker stimulation evokes activity in somatotopically organized barrel columns (for review, see Guy and Staiger, 2017). Conversely, mutations of transcription factors that alter the identity of cortical neurons, and of layer 4 neurons in particular, cause alterations in TC axon branching and formation of barrel patterns. The first example of such alterations was in cortex-specific deletion of the transcription factor *Lhx2*. TC axons were directed to the appropriate cortical region but did not form barrels (Shetty et al., 2013; Wang et al., 2017). A somewhat similar phenotype was recently observed in a cortex-specific deletion of the transcription factor *Rorα*, which is selectively expressed in layer 4 (Vitalis et al., 2018). Lhx2 and RORα control the expression of several guidance molecules, such as semaphorin7a and EphrinA5, that are expressed in layer 4 neurons and are important in the control of terminal branching of TC axons (Uziel et al., 2008; Carcea et al., 2014). Finally, a more severe disorganization of TC axons and complete disruption of the sensory map were noted in mutants of other transcription factors, such as *Ctip1*-KO mice (Greig et al., 2016). *Ctip1*- KO neurons were nonpermissive to TCA ingrowth but permissive to cortical callosal projections. Overall, these results indicate that molecular recognition and attraction cues are guided by timely and coordinated expression of transcription factors in thalamic and layer 4 neurons (Fig. 4).

Spontaneous activity in developing neural circuits of the whisker-barrel system

Mice and rats do not start whisking until the second postnatal week; but as the pups huddle, suckle, and move about, their snouts are stimulated. Trimming of whiskers, even at such early stages, causes behavioral alterations (Arakawa and Erzurumlu, 2015). Thus, even without whisking, passive tactile stimulation of whiskers is meaningful to the developing mouse brain. Indeed, more and more studies are finding that whisker deflections during early development evoke cortical activity, and these can be synchronized with spontaneous activity in thalamic neurons (Minlebaev et al., 2011; Akhmetshina et al., 2016). Moreover, spontaneous whisker movements in neonates, even while sleeping, can drive cortical activity (Khazipov et al., 2004; Tiriac et al., 2012). Extracellular and whole-cell recordings from the barrel cortex of neonatal rat pups revealed that there is a low level of tuning of presumptive barrel neurons to the principal whisker as early as PND0-PND1, before the barrels as neuronal clusters form (Mitrukhina et al., 2015). The same study further showed that a functional segregated whisker map emerges from PND2-PND3, in which individual neurons show preferential single whisker tuning.

Recently, Mizuno et al. (2018) adopted an elaborate strategy to image activity of layer 4 neurons *in vivo* in neonatal mice. They generated transgenic mice in which TC axons express RFP under control of the serotonin transporter promoter, which

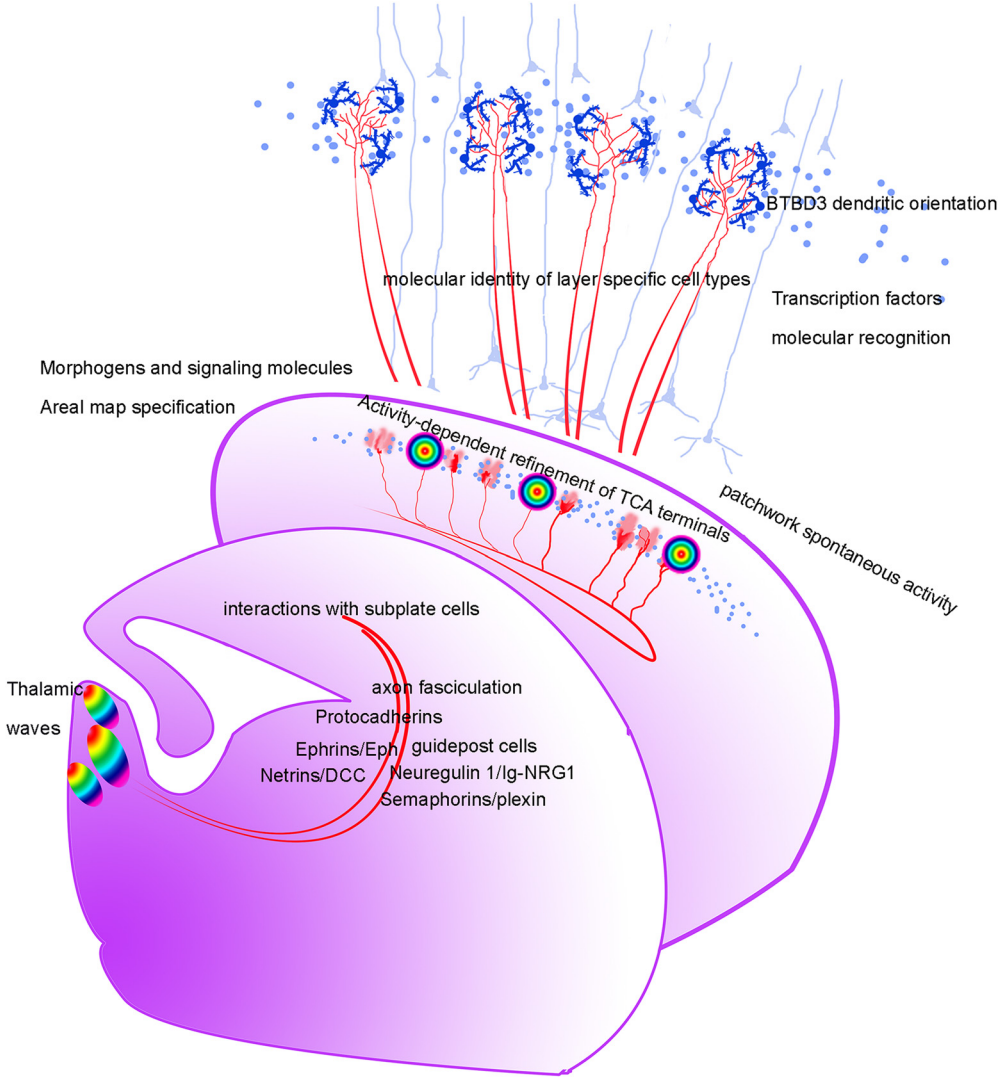

Figure 4. Diagram of the TC pathway and barrel formation in mice. Waves of calcium signals in the embryonic thalamus, schematically illustrated by graded colors, are suggested to correspond to a somatotopic connectivity between the thalamus and barrel cortex, before sensory input is present. Without these waves, barrel cortex becomes hyperexcitable and does not develop columnar and barrel organization (Antón-Bolaños et al., 2019). Developing TC axons are guided to cortex through multiple molecular guidance cues, some attractive and some repulsive (Antón-Bolaños et al., 2018). Morphogens and signaling molecules set up areal specification of the neocortex into primary sensory, motor, and association cortex areas (Fukuchi-Shimogori and Grove, 2001; Assimacopoulos et al., 2012; Zembrzycki et al., 2013, 2015; Stocker and O'Leary, 2016). In the developing barrel cortex, a patchwork of spontaneous activity corresponds to barrels at the time of their formation (Mizuno et al., 2018). Layer- and projection-type-specific identity of neocortical neurons is determined by their time of differentiation and specific transcription factors (Greig et al., 2013; Govidan and Jabaudon, 2017). Transcription factor RORα is cell-autonomously required in the thalamus for clustering of TC axons and dendritic maturation of layer 4 neurons in the barrel cortex (Vitalis et al., 2018). Dendritic orientation of barrel cells is controlled by the BTBD3 transcription factor (Matsui et al., 2013), and BTBD3 appears to be controlled by the transcription factor Lhx2 (Wang et al., 2017). So, transcription factors play multiple roles from cell specification to dendritic orientation in the barrel cortex.

labels these axons as described above to visualize barrel patterns, and they used *in utero* electroporation to express GCaMp6s in layer 4 neurons. They then analyzed spontaneous activity in relation to the barrels. They found that layer 4 neurons in the same barrel fire synchronously without peripheral stimulation, which the authors called "patchwork-type" spontaneous activity (Mizuno et al., 2018). Thus, even in the absence of peripheral sensory inputs, developing barrel neurons exhibit spontaneous correlated activity in a patterned ensemble.

Critical-period plasticity

Original studies on the barrel cortex (discussed earlier in this review) revealed that neonatal cautery of middle-row whisker follicles (row C) leads to shrinkage of the row C barrels into a thin, cigar-shaped band, and enlargement of barrels in neighboring rows B and D (Van der Loos and Woolsey, 1973; Woolsey and Wann, 1976; Belford and Killackey, 1979; Killackey and Belford, 1979; Woolsey et al., 1979). This effect occurs only if the follicle damage is done during the first few days after birth. Woolsey referred to this period as the "critical period" (Woolsey et al., 1979), whereas Belford and Killackey (1980) chose the term "sensitive period." In a review of critical, sensitive, vulnerable, and optimal periods in development, Erzurumlu and Killackey (1982b) pointed out: "The conceptual difference between the terms critical period and sensitive period is a very important one. The first denotes a period during which the presence of certain critical conditions is necessary for the nervous

system to develop normally and the other to a time during which damage to the nervous system can lead to alterations or reorganization of the system" (p. 208). The term "critical period" migrated to the whisker-barrel system from early monocular deprivation studies in the visual system (Wiesel and Hubel, 1963). In visual system critical-period plasticity, visual cortex is selectively deprived from inputs coming from one eye, without any retinal damage. In contrast, early injury to the whisker follicles or the infraorbital nerve, which innervates all the whisker follicles, interferes with the normal wiring of the central circuits. Despite emphasis on these fundamental differences between the two paradigms, the term "critical period" became more widely used in the field.

In pioneering experiments, Belford and Killackey (1980) concluded that the system was "sensitive" to follicle damage up to PND3 at all three stations: the brainstem, thalamus, and cortex in rats. This diverged from the conclusions of the Woolsey group of different "critical periods" for each station: the cortical one closing at PND6 and the thalamic one at PND4 in mice (Woolsey and Wann, 1976; Durham and Woolsey, 1984; Woolsey et al., 1979). Later studies (as discussed below) confirmed that, in both the rat and the mouse, the sensitive or critical period for anatomic plasticity closes by PND4.

To date, there is no clear understanding of what closes the critical period of morphologic plasticity induced in the rodent brain by whisker follicle damage. Several studies suggested that the barrel cortex critical period is tied to a developmental switch of cortical and thalamic expression of NMDA receptor subunits (Crair and Malenka, 1995; Celikel et al., 2004; Liu et al., 2004; Daw et al., 2006; Itami and Kimura, 2012; Itami et al., 2016). Curiously, however, a developmental switch in NMDA receptor NR2A/NR2B subunits does not occur in the developing trigeminal principal sensory nucleus in the brainstem, where plasticity resulting from follicle damage should first take place (Lo and Zhao, 2011). Furthermore, in NR2A KO mice, NMDA subunit composition and kinetics remain immature past the end of the critical period, but there is no extension in the closure of the critical period (Lu et al., 2001).

An early pharmacological blockade study led to the conclusion that NMDA receptors play an important role in determining the duration of the plasticity period in the rat barrel cortex (Schlaggar et al., 1993). However, a role for NMDA receptors in closing the plasticity period in barrel cortex was not confirmed in NMDA receptor KO mice (Datwani et al., 2002a). Thus, available data rule out an essential role for NMDA receptors in critical-period plasticity, at least during the developmental, morphologic critical period, which ends by PND4 in mice, even when mice are prematurely born (Toda et al., 2013). Despite the negative findings from KO mice with nonfunctional NMDA receptors, studies of the critical period in the barrel cortex expanded to explore processes that typically depend on NMDA receptors, including LTP, LTD, spike-timing-dependent plasticity, and expression of silent synapses.

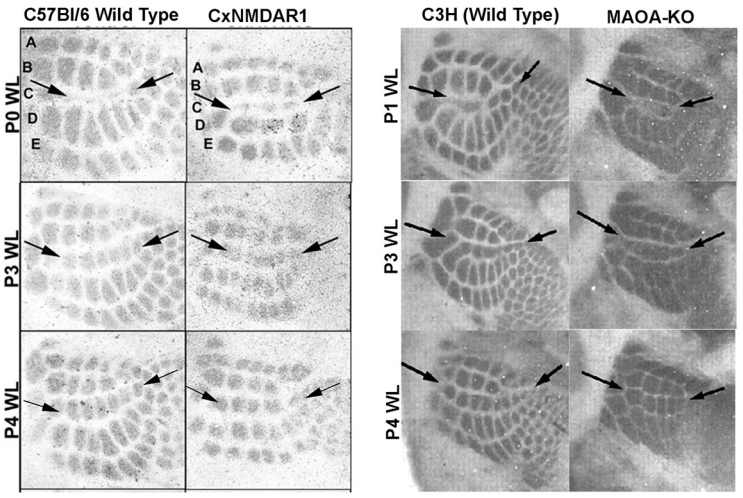

Figure 5. Developmental critical-period plasticity. Plasticity induced by row C lesion at three postnatal ages in two lines of WT and two lines of transgenic mice, one without functional NMDA receptors in the cortex and the other without monoamine oxidase A. Row C whisker-follicle lesions led to shrinkage of the row C barrels in the cortex and expansion of the neighboring rows B and D barrels, clearly noticeable by visual inspection without any quantification. Lack of functional NMDA receptors in the cortex does not change the duration of the critical period. That critical-period plasticity ends at P3, even in *MaoA* KO mice, when barrel formation in the cortex is delayed. Figure compiled from Datwani et al. (2002b) and Rebsam et al. (2005). Reprinted with permission from Rebsam et al. (2005).

Maoa KO mice allowed a different approach to test whether barrel cortex critical-period plasticity could be extended by delaying TC terminal patterning and barrel formation (Rebsam et al., 2005). In *Maoa* KO mice, excess 5-HT blocks patterning of TC axon terminals into whisker-specific patterns (Cases et al., 1996). Pharmacological treatment to reduce 5-HT levels permits formation of TC axon terminal patches. Rebsam et al. (2005) took this approach and delayed TC axon terminal patch formation by 3 d, and tested whisker lesion-induced plasticity. They found that, even when barrel formation is delayed by 3 d, the closure of whisker follicle injury-induced plasticity was unchanged (Fig. 5). These findings were interpreted as evidence favoring closure of the critical period in subcortical structures.

Overall, the factors governing the duration and expandability of the critical window during which the system is sensitive to peripheral damage are still unknown.

Other studies searched for critical periods in the true sense of sensory input deprivation, akin to visual system monocular deprivation, experimentally induced strabismus, or amblyopia. Most of these were done in rats by trimming all of the whiskers close to the fur, sparing a single whisker, leaving a pair of whiskers, or a mosaic of whiskers. They found expansion of the receptive fields of the barrel cells corresponding to the spared whiskers (Land and Simons, 1985; Fox, 1992, 2002; Diamond et al., 1994; Wallace and Fox, 1999; Trachtenberg et al., 2002; Allen et al., 2003). Experience-dependent cortical plasticity studies revealed multiple critical periods. More recent studies are expanding the concept of critical periods and barrel cortex plasticity to cellular and molecular levels involving neurons, glia, and endothelial cells (and adaptive changes at the molecular levels) (Kole et al., 2018).

Collectively, the above documented findings, and several others, are pointing to different forms of plasticity, sensitive periods, and critical periods during which damage to the sensory periphery or altered sensory experience along the whisker-barrel pathway can shape the morphology and function of cortical circuits throughout life.

Concluding remarks and future directions

Half a century of research on the rodent barrel cortex brought us amazing insights into cellular and molecular mechanisms of neural development and plasticity. What started with simple Nissl stains and crude fiber tracings evolved into finer and finer analyses as new techniques got introduced. Many studies in the field of development have used the rodent whisker-barrel pathway as a model system to study axon-pathfinding with a strong focus on TC (Antón-Bolaños et al., 2019) and tactile sensory circuits (Iwasato and Erzurumlu, 2018). Other developmental studies made use of the exquisite patterning of neurons and TC axons in the cortex to disentangle the mechanisms underlying activity-dependent remodeling of axons and dendrites (Erzurumlu and Gaspar, 2012) and the rules of cortical area specification and patterning (Simi and Studer, 2018). Manipulation of the mouse genome played a major role in this respect. Mouse genetics that initially started with a crude and labor-intensive approach in Lausanne in the late 1970s flourished with generation of numerous transgenic mouse lines. Molecular genetics allowed deleting or introducing genes in the different relays of the whisker-to-barrel pathway and thus identified transcription factors, neurotransmitters, and guidance molecules that are required for barrel formation. In the field of sensory physiology, the rodent barrel cortex took over the studies investigating many forms of plasticity, which were traditionally done in the visual system. Advances in optogenetics and *in vivo* imaging of neural activity in awake and behaving mice have found fertile ground for application in the barrel cortex to explore the underpinnings of sensory processing and plasticity. As our technology toolbox gets richer, barrel cortex will undoubtedly serve as a model for many years to come.

Some outstanding questions in the field of development still remain unanswered. The nature of the signal(s) derived from the sensory receptors that instructs a "one-to-one" mapping of individual whiskers along the trigeminal pathway (including when the routing of the axons is derailed) remains unknown. Despite five decades of research, we still do not know why inputs derived from one whisker cosegregate all along the sensory pathway and what could be the functional role of this discontinuous topographical organization for perception. Indeed, sensing the environment with whiskers implies an integration of signals rather than single whisker processing. The morphologic differences in barrel organization as cellular aggregates with hollow centers (mice) and cell-dense centers (rats) do not seem to matter much for whisker-sensory behaviors, as long as whisker-specific segregation of TC axons couples with aggregates of postsynaptic layer 4 cells. On the other hand, when the barrel patterning is diminished or absent as in *Ac1* KO, thalamus-specific *Ac1* or *Grin1* KOs, and in mice with a bifacial map with reduced barrel sizes for ipsilateral and contralateral whisker representations, whisker-dependent sensory discrimination and performance become impaired (Arakawa et al., 2014a,b; Tsytsarev et al., 2017).

A somewhat related question, which is now being actively explored, is how the segregated sensory inputs arriving to one barrel become distributed to other neurons of the sensory cortex (Egger et al., 2020) and other cortical and subcortical structures (Aronoff et al., 2010; Yamashita et al., 2018) to extract and synthesize/integrate useful information for sensorimotor processing (Petersen, 2019) and complex behavior (Yang et al., 2018).

Finally, the mouse barrel cortex is making advances in understanding cellular and molecular mechanisms underlying sensory and cognitive deficits associated with neurodevelopmental disorders, such as autism spectrum disorders, fragile X syndrome, and Rett syndrome, and diseases of aging, such as Alzheimer's disease and related dementias, as mouse models with associated genetic defects are made available (Crouzin et al., 2013; Beker et al., 2016; Lo et al., 2016a,b; Maatuf et al., 2016; Lee et al., 2017; Lo and Erzurumlu, 2018; Booker et al., 2019; Domanski et al., 2019). Tactile sensory abnormalities or altered sensitivities are common features of both neurodevelopmental disorders and dementias. Cortical circuits that connect the primary somatosensory areas with frontal cortical association areas are gaining increased interest in understanding how these circuits subserving sensory perception and cognition are altered at the molecular and circuit level in mouse models of these conditions. Clearly, new insights will come out of these studies in the near future.

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