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Development and Critical Period Plasticity of the Barrel Cortex

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Abstract

In primary sensory neocortical areas of the mammals, the distribution of sensory receptors is mapped with topographic precision and amplification in proportion to the peripheral receptor density. The visual, somatosensory and auditory cortical maps are established during a critical period in development. Throughout this window in time, the developing cortical maps are vulnerable to deleterious effects of sense organ damage or sensory deprivation. The rodent barrel cortex offers an invaluable model system to investigate mechanisms underlying the formation of topographic maps and their plasticity during development. Five rows of mystacial vibrissa (whisker) follicles on the snout and an array of sinus hairs are represented by layer IV neural modules (“barrels”) and thalamocortical axon terminals in the primary somatosensory cortex. Perinatal damage to the whiskers or the sensory nerve innervating them irreversibly alters the structural organization of the barrels. Earlier studies emphasized the role of sensory periphery in dictating whisker-specific brain maps and patterns. Recent advances in molecular genetics and analyses of genetically altered mice allow new insights into neural pattern formation in the neocortex and the mechanisms underlying critical period plasticity. Here we review the development and patterning of the barrel cortex and the critical period plasticity.

Keywords

cerebral cortex; trigeminal system; synaptic plasticity; whiskers; pattern formation; sensory deprivation; thalamus; activity-dependent mechanisms

The barrel cortex

In the primary somatosensory cortex of mice, layer IV neurons form cylindrical aggregates replicating the patterned array of whiskers on the contralateral snout. Rafael Lorente de Nó (1922) noted these cellular aggregates in layer IV of Golgi-stained mouse cortex and called them ‘glomérulos’ without localizing them to the somatosensory cortex (Fairén, 2007). Almost fifty years later Thomas A. Woolsey (1967) studied the mouse sensory cortex and associated Lorente de Nó’s glomeruli with whiskers. A few years later extensive studies performed by Thomas A. Woolsey and Hendrik Van der Loos (Woolsey and Van der Loos, 1970; Van der Loos and Woolsey 1973) revealed a one-to-one association of individual whiskers on the snout with cortical cellular aggregates, which they termed “barrels.” Around the same time, Herbert P. Killackey (1973), using anterograde axonal degeneration method,

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showed that in the rat, the barrels are filled with axon terminals arising from the ventroposteromedial (VPM) nucleus of the thalamus. Later studies in both species confirmed and detailed that layer IV stellate cells form the “barrel walls” and discrete patches or “bouquets” of VPM axon terminals fill them up (Killackey & Leshin, 1975; Erzurumlu & Jhaveri, 1990; Senft & Woolsey, 1991; Agmon *et al.*, 1993; Rebsam *et al.*, 2002).

The dendrites of barrel cells are preferentially oriented towards the barrel centers and embrace the thalamocortical terminals within the barrels (Woolsey *et al.*, 1975, Steffen & Van der Loos, 1980; Jeanmonod *et al.*, 1981; Datwani *et al.*, 2002a). Pioneering electrophysiological recordings revealed that each barrel receives and processes information predominantly from a single whisker (Welker, 1971, 1976). Ensuing physiological studies consistently reported that neurons located within individual barrel columns are mostly responsive to deflection of the associated whiskers on the contralateral snout (Simons, 1978; Chapin & Lin, 1984; Simons, 1985; Armstrong-James & Fox 1987; Simons & Carvell, 1989; Armstrong-James *et al.*, 1992; also reviewed in Petersen, 2007; Fox, 2008).

The distribution of barrels is best seen in tangential sections through the layer IV. The spatial arrangement of these neural modules across layer IV replicates that of the whiskers and sinus hairs on the snout. A similar but less distinct barrel-type patterning is present in the cortical areas representing the lower jaw, forepaw and hindpaw pads (Belford & Killackey, 1978; Dawson & Killackey, 1987; Killackey *et al.*, 1995). When the mouse or rat cortex is flattened (Strominger & Woolsey, 1987; Dawson & Killackey, 1987), the entire face and body map and the barrel fields appear as a “musculus” or “ratunculus.” Today, the flattened cortex preparation is widely used to assess any alterations in patterning of the barrel cortex.

Development of subcortical whisker-specific neural patterns and the barrels in the cortex

The pioneering whisker follicle lesion studies of Van der Loos & Woolsey (1973) showed that each barrel corresponds to a single whisker on the contralateral face. The presence of whisker patterns in the subcortical structures and their malleability following whisker lesions were discovered later on (Van der Loos, 1976; Belford & Killackey 1979; 1981; Durham & Woolsey, 1984). The whisker-specific neural patterns in subcortical structures have been named “barreloids” in the VPM-VPL complex of the thalamus (Van der Loos, 1976) and “barrelettes” in the brainstem (Ma & Woolsey, 1984).

The topographic organization of the barrels in the neocortex is fashioned after the distribution of five rows of whiskers, each row with constant number of follicles. The infraorbital nerve (ION) of the maxillary division of the trigeminal nerve innervates all of the whiskers and sinus hairs on the whisker and furry buccal pads. Central axons of the trigeminal ganglion (TG) neurons contributing to the ION convey whisker-specific information to the trigeminal brainstem nuclei. Of these brainstem nuclei, the principal sensory nucleus of the trigeminal nerve (PrV) plays the main role in transferring whisker-specific patterning to the contralateral thalamus, the VPM nucleus (Killackey & Fleming, 1985). At each level of the central whisker pathways the afferent terminals are the first elements to form whisker-specific patterning. Barrelette cells in the brainstem, barreloid cells in the thalamus, and barrel cells in the cortex all develop a patterned organization of their dendrites after the clustering of presynaptic afferents. Furthermore, the pattern formation follows a sequential order from the periphery to the brainstem to the thalamus and finally the neocortex during the first few days after birth (reviewed in Sehara & Kawasaki, 2011; Figure 1, Table 1).

Whisker-specific patterning in the brainstem emerges by embryonic day (E)19-20 in the rat (Chiaia *et al.*, 1992a; Waite *et al.*, 2000), and at birth (P0) in mice (Ma, 1993; Figure 1, Table 1). From the earliest time of target invasion, terminal ION arbors have synaptically active boutons and the postsynaptic responses in the PrV show a predominant NMDA component (Waite *et al.*, 2000). Polarized, asymmetrical dendritic orientation and whisker-specific patterning characterize the barrelette neurons. These small diameter cells display a transient K^+ (I_A) current and receive monosynaptic excitatory and disynaptic inhibitory inputs upon stimulation of the trigeminal tract (Lo *et al.*, 1999).

The barrelette cells are also the trigeminothalamic projection cells (Erzurumlu *et al.*, 1980). Their axons cross the midline, collect along the medial lemniscus, forming the trigeminal lemniscus. In the mouse, PrV neurons are derived from the rhombomeres 2 and 3 (Oury *et al.*, 2006). Newly differentiated PrV neurons send axons across the midline at E11, as they are migrating to the presumptive PrV (Figure 1). These axons make a sharp rostral turn as soon as they traverse the midline and elongate rostrally towards the contralateral thalamus (Kivrak & Erzurumlu, 2012). The trigeminal lemniscus reaches the VPM by E17. These afferents initially develop expansive arbors within the boundaries of the VPM, which gradually coalesce into whisker row-specific curvilinear columns followed by single whisker-specific patches during the first few days after birth (Kivrak & Erzurumlu, 2012). Cellular patterns (barreloids) follow afferent patterns and are apparent by P3 (Figure 1). Axon guidance molecules netrin1 and slit proteins play a major role in guiding the initial formation of the trigeminal lemniscus (Mirza *et al.*, 2012), but molecular guidance cues attracting and confining lemniscal axons to the VPM are not yet fully understood. The molecular mechanisms of pattern formation in the brainstem have been reviewed elsewhere (Erzurumlu *et al.*, 2006; 2010; see also Pouchelon *et al.*, this issue). In contrast to the development of terminal arbor patterning in VPM from initially diffuse to patchy, in both the upstream PrV and the downstream barrel cortex, whisker-related afferents develop topographically ordered terminal fields from the onset (Catalano & Killackey, 1991; Agmon *et al.*, 1993; 1995; Waite *et al.*, 2000; Lee *et al.*, 2005a, b; but see Senft & Woolsey 1991 and Rebsam *et al.*, 2002 for cortex).

Two decades ago, simultaneous labeling of thalamocortical axons, serotonergic raphe-cortical projections, postsynaptic cells, extracellular elements revealed that the whisker-specific patterning first occurs in the terminal arbors of the thalamocortical axons and other elements are patterned afterwards (Erzurumlu & Jhaveri, 1990; 1992b, Jhaveri *et al.*, 1991; Blue *et al.*, 1991). The whisker-specific patterning of thalamocortical terminals emerges during the 3 days after birth, first by formation of rows and then breaking up into individual whisker follicle representations (Erzurumlu & Jhaveri, 1990; Rhoades *et al.*, 1990; Senft & Woolsey, 1991; Agmon *et al.*, 1993; Rebsam *et al.*, 2002; Lee *et al.*, 2005b).

The early patterning of thalamocortical axons is dependent on the sensory periphery. This has been amply demonstrated by lesion studies performed in perinatal rodents (Van der Loos & Woolsey, 1970; Belford & Killackey, 1981; Durham & Woolsey, 1984; Bates & Killackey, 1985; Dawson & Killackey, 1987; Jensen & Killackey, 1987; Killackey & Dawson, 1989). Furthermore, in mice, selectively inbred for abnormal, additional whisker follicles (supernumerary whiskers) at different loci in the whisker pad, corresponding extra barrels formed in the somatosensory cortex (Van der Loos *et al.*, 1984; 1986; Welker & Van der Loos, 1986). These and other lines of evidence, e.g., rerouting of visual pathways to the auditory cortex or visual pathways to the somatosensory cortex (Métin & Frost, 1989; Roe *et al.*, 1990; Sur *et al.*, 1990; Pallas, 2001) were interpreted as areal specification of the neocortex by incoming thalamic afferents (O'Leary, 1989; O'Leary *et al.*, 1994). A recent study added another example of peripheral guidance of central patterns. Ephrins are expressed in a gradient along the developing whisker pad and in *EphA4* knockout mice

several ventroposterior whisker follicles are missing; consequently corresponding barrels in the caudal portions of rows D and E are also missing, as are the relevant subcortical patterns (North *et al.*, 2010).

Areal specification of the barrel cortex

In 1994, an enhancer trap transgenic mouse line was produced in which beta-galactosidase expression was confined to layer-IV neurons of the primary somatosensory cortex (Cohen-Tannoudji *et al.*, 1994). Heterotopic transplantation experiments further confirmed that this transgene (*H-2ZI*) is intrinsic to the neocortex and specific to the somatosensory region (Cohen-Tannoudji *et al.*, 1994; Gitton *et al.*, 1999a). These observations raised the possibility that the formation of the barrel cortex is guided by intrinsic cortical cues. The pattern of *H-2ZI* expression in cortical explants in reeler and monoamine oxidase A (MAOA) deficient mice and in mice with neonatal whisker or thalamic lesions revealed that *H-2ZI* expression develops autonomously and does not require sensory inputs from the periphery; but it is also under the influence of thalamic signals once these axons arrive in the cortical plate, as expression is strongly reduced by early thalamic lesions (Gitton *et al.*, 1999b). Since then, genetic loss-of-function/gain-of-function and molecular profiling studies of the developing neocortex have revealed a complex interaction of numerous morphogens and transcription factors in localization of cortical maps, their orientation and size.

Signaling molecules such as fibroblast growth factor 8 (FGF8), bone morphogenetic proteins (BMPs), vertebrate orthologs of *Drosophila* wingless (WNTs), sonic hedgehog (SHH) are expressed from cortical patterning centers in a gradient and they define the topological coordinates of the cortical mantle and positioning of future territories of sensory and motor thalamocortical projections (Shimogori & Grove, 2006; Sur & Rubenstein, 2005; O'Leary & Sahara, 2008). For example, FGF8 is normally expressed in the anterior commissural plate and ectopic expression in the posterior cortex by in utero electroporation leads to mirror image, partial duplication of the whisker barrel maps (Fukuchi-Shimogori & Grove, 2001). Morphogens secreted by organizing centers of the cortical mantle (i.e., commissural plate, cortical hem) define areal fate by regulating differential expression of a variety of transcription factors in cortical progenitors.

Parcellation of SI body map and incoming thalamocortical afferents

While the areal specification of cortical maps is largely determined by intrinsic genetic programming of the neocortex, neural activity plays a role in allocation of cortical tissue to different components of the somatosensory body map. In mice with genetically reduced NMDA receptor function, the PrV in the brainstem shrinks and fails to develop barrelette patterns even though a full complement of whiskers is present on the snout (Lee & Erzurumlu, 2005). The downstream effects are absence of barreloids in the VPM and barrels in the face region of the neocortex and shrinkage of the overall face representation area in comparison to forepaw and hindpaw regions with digit-specific neural patterns and barrels (Lee & Erzurumlu, 2005).

Studies in mice with targeted gene deletions have identified several transcription factors that control thalamocortical development. These include *Emx2*, *Tbr1*, *Gbx2*, *Mash1*, *Ebf1*, *Foxg1* and *Pax6*. In null mutations of *Gbx2*, *Mash1*, *FoxG1* or *Pax6* thalamic axons fail to innervate the neocortex (Lopez-Bendito & Molnar, 2003; Pratt & Price 2006; Price *et al.*, 2006; also other articles in this issue). Transcription factors *Lhx2*, *SCIP*, and *Emx1* and cadherins *Cad6*, *Cad8*, and *Cad11* are all expressed in areal patterns independent of thalamocortical innervation, as seen in *Mash-1* mutant mice which fail to develop a TCA projection (Nakagawa *et al.*, 1999). A variety of axon guidance cues and growth-associated proteins also play roles during target-directed growth and invasion of thalamocortical axons.

For example, Ephrins and their Eph receptors have been implicated in precision of patterning within topographically organized cortical face map (reviewed in Vanderhaeghen & Polleux, 2004; Uziel *et al.*, 2006). GAP-43, a growth-associated phosphoprotein, is transiently expressed by developing thalamocortical axons and the thalamocortical topography is severely disrupted in *GAP43* knockout mice (Erzurumlu *et al.*, 1990; Maier *et al.*, 1999). The numbers of experimentally identified intrinsic cortical and thalamic molecular cues are mounting. However, there is no evidence of sensory periphery-related topographic organization and patterning of the neocortex independent of thalamic innervation. Many studies point out to presence of distinct mechanisms underlying topographic ordering and periphery-related patterning along every station of the somatosensory pathway.

During their target-directed growth phase, thalamocortical axons interact with subplate (SP) neurons, which are some of the earliest generated cortical neurons and reside just above the white matter (reviewed in Kanold & Luhman, 2010). SP neurons form a scaffold for the developing reciprocal thalamocortical projections. Neurites arising from SP neurons are confined to barrel hollows during P4-6 and their patterned organization also appears to depend on an intact sensory periphery (Pinon *et al.*, 2009).

Role of neural activity in patterning of the barrel cortex

Once the cortical territories are assigned to incoming thalamocortical axons and they are guided by molecular cues to their targets, neural activity plays a major role in patterning of the cortical sensory maps. Communication between thalamocortical axons and their postsynaptic partners occurs via glutamatergic neural transmission and it is regulated by monoamines (such as serotonin) and GABAergic inhibitory influences from local circuit neurons (Erzurumlu & Kind, 2001). As noted above, various forms of manipulations of the sensory periphery during a critical window in development induce plastic changes in the size and patterning of pre and postsynaptic elements in the barrel cortex.

In early studies, pharmacological blockade of action potentials or N-Methyl-D-Aspartate (NMDA) receptors, either in the neocortex or in the ION, did not affect cortical patterning (Chiaia *et al.*, 1992b; Henderson *et al.*, 1992; Schlaggar *et al.*, 1993). However, later pharmacological blockade experiments noted significant alterations in single whisker responsiveness of barrel neurons and functional organization of cortical columns (Fox *et al.*, 1996) and in the morphological integrity of barrels (Mitrovic *et al.*, 1996). In spite of the inconsistent results from pharmacological perturbation studies, our current understanding of the role of activity in barrel formation comes from targeted gene manipulations in mice.

Genetic loss of function studies in mice revealed that NMDARs, metabotropic glutamate receptors, and altered levels of cortical serotonin (5-HT) yield defective barrel cortex phenotypes (reviewed in Erzurumlu & Kind, 2001; Erzurumlu & Iwasato, 2006; Inan & Crair, 2007; Wu *et al.*, 2011).

Selective loss of the *NR1* gene in cortical excitatory neurons genetically blocks NMDAR activity in the neocortex (Iwasato *et al.*, 2000). In these mutants (*CxNR1* knockout mice), the whiskers on the snout and all subcortical whisker-related patterns are similar to those seen in wild type mice but barrels as cellular aggregations are missing, the dendritic field bias of layer IV spiny stellate cells (barrel cells) is lost, and the thalamocortical axons form exuberant terminal arbors within which there is some clustering, i.e., rudimentary whisker-specific patterning (Iwasato *et al.*, 2000; Datwani *et al.*, 2002a; Lee *et al.*, 2005a). Similar barrel cortex defects were also reported in genetically altered mice with defects in other components of the glutamatergic pathway such as metabotropic glutamate receptor 5

(mGluR5) and PLC β (phospholipase C- β) (Hannan *et al.*, 1998; 2001; Ballester-Rosado *et al.*, 2010).

Cortical 5-HT augmentation (but not depletion) also affects barrel development (see Van Kleef *et al.*, this issue). Initial pharmacological blockade experiments used p-chloroamphetamine (PCA), a selective 5-HT neurotoxin in postnatal rats and uncovered a delay in barrel formation (Blue *et al.*, 1991), but a more dramatic effect was achieved in mice with 7–9-fold increase in 5-HT levels following disruption of the *monoamine oxidase A* (*Maoa*) gene. In *Maoa* knockout mice the thalamocortical axon terminal segmentation was completely blocked and barrels did not form, even though the whiskers on the snout and related patterning in the brainstem and thalamus were normal (Cases *et al.*, 1996). Clorgyline (an MAOA inhibitor) administration during the postnatal period in wild type mice also mimicked the barrel cortex phenotype seen in the *Maoa* knockout mice (Cases *et al.*, 1996; Vitalis *et al.*, 1998). During a transient period in development the thalamocortical axons express 5-HT_{1B} receptors (Bennett-Clarke *et al.*, 1993) and the VPM neurons express the serotonin and the vesicular monoamine transporters (SERT/5-HTT/S16a4 and VMAT2) (Lebrand *et al.*, 1996, 1998). *5-HTT* knockout mice show partial patterning in the barrel cortex and thalamocortical axon patterning is severely disrupted in *Maoa* and *5-HTT* double knockout mice. Genetic removal of 5-HT_{1B} receptors in *Maoa*, *5-HTT* knockout mice or in *Maoa/5-HTT* double knockout mice rescue the defects and both the thalamocortical axons and layer IV cortical cells form barrels (Salichon *et al.*, 2001). The precise role of 5-HT in normal barrel development is still not clear (see Van Kleef *et al.*, this issue for discussion). Electrophysiological recordings from thalamocortical slices indicated that 5-HT has a strong presynaptic inhibitory effect at the thalamocortical synapse (Rhoades *et al.*, 1994; Laurent *et al.*, 2002). During thalamocortical development, 5-HT_{1B}-mediated signaling plays a multifaceted role, including autoregulation of glutamate release (Rhoades *et al.*, 1994; Laurent *et al.*, 2002), axonal growth (Lotto *et al.*, 1999) and response to guidance molecules such as netrin 1 (Bonnin *et al.*, 2007). However, pharmacological or genetic 5-HT depletion does not affect barrel formation other than a couple of days delay, which may be related to growth retardation (Van Kleef *et al.*, this issue) and does not affect the duration of the critical period plasticity which follows neonatal whisker follicle damage (Blue *et al.*, 1991; Osterheld-Haas and Hornung, 1996; Turlejski *et al.*, 1997).

A spontaneous mouse mutant with a “barrelless” (*brl*) phenotype was identified in Lausanne (Welker *et al.*, 1996). The mutation was later identified as a transposon insertion in the Adenylyl cyclase type I gene (*AC1*) (Abdel-Majid *et al.*, 1998). In *brl* (or *AC1* knockout) mice, thalamocortical axon arbors are broader and cellular barrels do not form (Welker *et al.*, 1996; Gheorghita *et al.*, 2006). The peripherally evoked synaptic responses of presumptive barrel cortex neurons are also abnormal with a prominent disruption of AMPA receptor surface expression and long-term potentiation (LTP) and long-term depression (LTD) in layer IV neurons (Welker *et al.*, 1996; Lu *et al.*, 2003). AC1 is a member of Adenylyl cyclases, it catalyzes the formation of cAMP and it is stimulated by guanine nucleotide-binding protein (Gs) coupled receptors and by Ca² influx through voltage-sensitive Ca² channels (reviewed in Hall & Cooper, 2011)

Br1 mouse as a global *AC1* knockout displays subcortical pattern defects. Cortex-specific AC1 deletion led to a much less severe barrel cortex phenotype (Iwasato *et al.*, 2008). While minor alterations were noted in barrel cortex organization and postsynaptic function, gross morphological features and critical period plasticity were not altered suggesting that loss of presynaptic rather than postsynaptic AC1 function might be the major cause of defects seen in the *brl* mice.

Structural and functional defects were also observed in the barrel cortex of mice lacking one of the regulatory subunits (PKARII β) of PKA, a signaling molecule downstream from AC1 (Inan *et al.*, 2006; Watson *et al.*, 2006). These mice have postsynaptic defects in cellular organization and lack of LTP in layer IV; however, the thalamocortical axon patterning in these animals is present. Since PKARII β is postsynaptic the observed pattern deficits confirm the conclusion that the barrels as layer IV cellular aggregates can be perturbed independently of afferent patterning (Inan *et al.*, 2006; Watson *et al.*, 2006).

Involvement of presynaptic mechanisms in barrel formation was inferred from studies on *monoamine oxidase A* (*Maoa*; Rebsam *et al.*, 2002), *AC1* (Gheorghita *et al.*, 2006) and *RIM1a* (Lu *et al.*, 2006) knockout mice. A more recent study compared the effects of thalamic or cortical ablation of RIM1 and RIM2 proteins on barrel formation (Narboux-Nême *et al.*, 2012). RIM proteins are located at the presynaptic active zone and control synaptic vesicle exocytosis (Deng *et al.*, 2011; Kaeser *et al.*, 2011). Thalamus-specific deletion of both RIM1 and RIM2 reduced neurotransmission efficacy by 67 % but did not affect whisker-specific patterning of thalamocortical axon terminals, albeit reduction in patch sizes (Narboux-Nême *et al.*, 2012). On the other hand, in contrast to cortex-specific deletion, thalamus-specific deletion of RIMs yielded a barrelless phenotype with alterations in the dendritic orientation of layer IV neurons (Narboux-Nême *et al.*, 2012). This underscores the importance of presynaptic thalamocortical mechanisms rather than cortico-cortical synapses in dendritic orientation of neurons in layer IV. Thus, at the thalamocortical synapse, both pre- and postsynaptic mechanisms are involved in barrel formation. Structural and functional defects in barrels often result from defective patterning of thalamocortical axons (see Wu *et al.*, 2011 for a recent review). To date, no mouse mutants have been identified with a failure in thalamocortical axon terminal patterning but with a “normal” complement of barrels.

Critical Period Plasticity in the developing “whisker-barrel” pathway

Early sensory experience shapes the morphological and functional organization of developing brain circuits. Competition between synaptic inputs, balance between excitation and inhibition, interactions with the extracellular matrix environment all play roles in wiring of the brain during sensory system development (Hensch, 2004, 2005). Since the classical visual deprivation studies of Hubel & Wiesel (1964), it has been well established that the occlusion of one eye early in life leads to irreversible loss of visual acuity through the deprived eye (Daw 1995; Prusky & Douglas, 2003; Wiesel, 1982). Unbalanced visual experience and activity-dependent competition between eye-specific inputs lead to a rapid shift of neuronal responses in the primary visual cortex in favor of the open eye and this period of cortical malleability is known as the critical period for ocular dominance (Antonini *et al.*, 1999; Hensch, 2005; Wiesel & Hubel, 1963). The concept of “critical period” indicates a time period during which the presence of specific external or internal condition is necessary for normal development and that the absence of such condition leads to irreversible alterations in the organism (Erzurumlu & Killackey, 1982). The critical period concept for the whisker-barrel pathway was inspired by ocular dominance plasticity studies of Hubel and Wiesel (Belford & Killackey, 1980; Durham & Woolsey, 1984; Van der Loos & Woolsey, 1973; Erzurumlu, 2010). However, there are significant differences between the development and the organization of these two sensory systems as well as in the sensory deprivation paradigms used. Occlusion of an eye by lid suture blocks natural visual stimulation without any damage to the retina and the visual pathways. Whisker follicle lesions or ION transection physically damages the sensory apparatus. Thus, “plasticity” as manifest in aberrant organization of the trigeminal pathway and the barrel field is a reflection of the vulnerability of the developing system to physical damage during its wiring rather than the critical nature of the sensory experience. Initially, the term “sensitive period”

was used to describe structural alterations along the trigeminal pathway following neonatal whisker damage (Belford & Killackey, 1980). However, the term “critical period plasticity” has been widely adopted in reference to structural or functional or behavioral changes that take place following neonatal sensory peripheral damage or simple whisker trimming. Because of this, and due to differential effects of a variety of peripheral sensory manipulations on different cortical layers at morphological or functional levels, multiple critical periods have been delineated (Fox, 2002). In fact, such a wide concept of plasticity encompasses all forms of structural and functional malleability in the somatosensory cortex throughout life. In this review, we focused on developmental plasticity of the barrel cortex, seen during the first few postnatal weeks of life.

Rodent pups are born with a full set of fine whisker hairs that are curved back and are immobile. Active “whisking” behavior starts at the end of the second postnatal week, just before eye opening (Landers & Ziegler, 2006). Trigeminal ganglion cells are responsive to whisker stimulation before the onset of whisking (Shoykhet *et al.*, 2003) and neonatal rats respond to whisker stimulation, and display tactile learning in a classical conditioning avoidance paradigm (Landers & Sullivan, 1999; Sullivan *et al.*, 2003). Facial tactile experience of newborn rodent pups is mostly limited to physical contacts with their littermates and their mother. Whisker trimming between postnatal days 3–5 disrupts nipple attachment and huddling behaviors (Sullivan *et al.*, 2003). Clearly morphological, physiological and behavioral maturation of the whisker-barrel system depends on sensory evoked activity during the postnatal life. However, as will be discussed below most of the “sensory deprivation” experiments in the whisker to barrel pathway consisted in lesioning the whisker follicles or the nerves. Whisker cautery or ION lesions clearly block peripherally evoked afferent activity along the pathway in addition to transsynaptic cell death and possible communication via yet to be identified “trophic” factors. Whisker plucking on the other hand, leads to lessened sensory activity but does not completely block it as the neonatal rodent pup gets its sensory receptors on the snout stimulated during huddling and suckling. Active whisking does not start until two weeks of age (Landers & Ziegler, 2006; Welker, 1964), the role of passive stimulation of developing whiskers and their follicles in shaping up the brain circuitries during a short period in postnatal development is still poorly understood.

The spatial arrangement of whisker and sinus hair follicles on the snout provides a template for the formation of axonal and cellular patterns in the barrel cortex during a critical period in development. Five curvilinear arrays (rows A–E) of whisker follicles emerge before neurogenesis of the trigeminal ganglion or any other central trigeminal targets (Davidson & Hardy, 1952; Yamakado & Yohro, 1979; Van Exan & Hardy, 1980; Stainier & Gilbert, 1990). Whisker follicle cautery or lesions of the ION before P4 irreversibly alter the organization of central neural patterns. The classical example is from the original Van der Loos and Woolsey 1973 study where they electrocauterized the follicles of the middle row whiskers (row C) on the day of birth and observed that cortical barrels corresponding to row C whiskers shrunk (Figure 2). Fusion of the lesioned row C barrels and expansion of the neighboring rows D and E barrels have been demonstrated at the thalamocortical axon terminal, layer IV cortical cell and dendritic orientation levels for mice and rats (Woolsey & Wann, 1976; Belford & Killackey, 1980; Jeanmonod *et al.*, 1981; Figure 2). If the whisker pad is completely denervated of its sensory input by ION transection, no barrels are seen in the cortex and the thalamocortical axons are distributed in an aberrant fashion (Belford & Killackey, 1980; Bates & Killackey, 1985; Jensen & Killackey, 1987). A similar defect in the dorsal column lemniscal pathway is also noted following embryonic paw amputations (Dawson & Killackey, 1987; Killackey *et al.*, 1995). In contrast to physical damage to whisker follicles or the ION, simple whisker trimming or plucking in neonates do not alter the development of whisker-specific central patterns at the gross morphological level but has

other consequences such as reducing dendritic complexity and spines of barrel neurons or the behavioral repertoire of the animal later on (Lee *et al.*, 2010).

Studies in rats and mice revealed that physical perturbation of the whisker follicles or the ION during a window of time in perinatal development leads to irreversible structural alterations in the patterning of the whisker-related neuronal circuits (Figure 2); this period abruptly ends by P4 (Van der Loos & Woolsey, 1973; Belford & Killackey, 1980; Durham & Woolsey, 1984). A recent study challenged the notion that sensory experience-dependent structural plasticity is confined to the first few days after birth. Thalamocortical axons arising from the VPM and/or posteromedial (POm) nucleus were labeled with virus-mediated fluorescent proteins and their distribution was examined after trimming all the whiskers except one or two for a period of P0-P96 (Wimmer *et al.*, 2010). Whisker trimming induced about 30% decrease in the density of VPM axons in deprived cortical columns and these effects were reversible after regrowth of the trimmed whiskers, independent of the age at deprivation. No change was detected in POm projections. The differential effects of whisker follicle cautery and whisker trimming have been long noted and perhaps the notion of critical period should be evaluated differently depending on whether sensory deprivation is achieved through whisker trimming only or it also includes damage to the primary sensory neurons involved in mediating the sensory experience.

In the newborn rat, damage to the ION results in synaptic remodeling in the PrV. Trigeminal afferent patterning is lost and barrelette cell dendritic trees assume nonspecific symmetric distribution (Lo & Erzurumlu, 2002). Neonatal ION damage also leads to a significant apoptosis in the TG, the PrV and the VPM (Miller *et al.*, 1991; Miller & Kuhn 1997; Sugimoto *et al.*, 1998, 1999; Baldi *et al.*, 2000). Despite significant cell loss, membrane properties of surviving PrV neurons, neurotransmitter release probability of trigeminal afferents and postsynaptic NMDA receptor subunit composition do not change (Lo & Erzurumlu 2001, 2011; Lo & Zhao 2011). However, postsynaptic responses of denervated PrV neurons are mostly silent synapses without functional AMPA receptors (Lo & Erzurumlu 2007). The molecular and functional changes at the first relay station of the PrV set the stage for pattern defects downstream in the VPM and the barrel cortex.

Another important caveat in whisker lesion-induced plasticity of the barrel cortex is that the whisker-specific patterning in the VPM and the barrel cortex is still under construction during the critical period. In other words, the so called “plastic” changes are not reorganization of already patterned presynaptic afferent terminals and oriented dendritic trees of postsynaptic cells but aberrant development of these elements from the onset in response to physical damage to the sensory periphery.

In search of axonally transported chemical signals

How does the disruption of the sensory periphery alter afferent clustering and dendritic organization of barrel cells across synapses? Molecular underpinnings of barrel cortex plasticity and its confinement to a critical period in development have been long sought. In this context two lines of thought have directed the search for molecular mechanisms of barrel cortex plasticity: Axonal transport of chemical signals and peripherally evoked activity (or lack of it) along the trigeminal pathway leading to the barrel cortex. Inhibition of trigeminal axonal transport with colchicine- or vinblastine impregnated implants in neonatal rats resulted in the absence of whisker-related cytochrome oxidase patterns in the PrV, VPM and the barrel cortex (Chiaia *et al.*, 1996) but Na⁺ channel blockade with TTX or NMDA receptors with APV did not (Chiaia *et al.*, 1992b; 1994; Henderson *et al.*, 1992). These results suggested that chemical signals conveyed from the whisker follicles to the brainstem and transsynaptically onto the barrel cortex are necessary for the development of whisker-

specific central neural patterns. An overlooked finding of the axonal transport blockade study is the fact that the pharmacological agents used also caused 90% reduction in TG cells (Chiaia *et al.*, 1996).

Nerve growth factor (NGF) family of neurotrophins promotes survival and differentiation of primary sensory neurons and they are abundant in the developing whisker pad. Thus, they have been the prime candidates for patterning of the trigeminal pathway. In the mouse barrel cortex, neurons express brain-derived neurotrophic factor (BDNF) and *trkB* mRNA (Lush *et al.*, 2005) and the expression levels decrease following row C cautery in newborns (Singh *et al.*, 1997). A transient increase in BDNF mRNA levels has been detected in the barrel cortex following whisker stimulation (Rocamora *et al.*, 1996). In *BDNF* knockout mice, thalamocortical synaptic communication is impaired (Itami *et al.*, 2000). Barrel patterns form but thalamocortical patterning is delayed in both the BDNF and *TrkB* knockout mice (Lush *et al.*, 2005). In another related study, gelfoam impregnated with NGF, BDNF or neurotrophin-3 (NT-3) was placed under the whisker pad following whisker row nerve transection (Calia *et al.*, 2001). This study found that BDNF and NT-3 rescued development of the cortical barrels corresponding to the denervated whiskers and prevented the lesion-induced expansion of neighboring barrels of the intact whiskers (Calia *et al.*, 2001). Application of BDNF and NGF to the damaged ION also rescues many VPM neurons from transneuronal death (Baldi *et al.*, 2000). It is highly likely that peripheral infusion of neurotrophins acts first in the TG and prevents cell death in this experiment. This might then lead to maintenance of whisker patterns by the central trigeminal afferents and all along the pathway leading to the barrel cortex. Cortical levels of NGF, BDNF or NT-3 do not appear to play a major role in initial pattern formation and duration of the critical period plasticity. This conclusion is further supported by the presence of whisker-specific patterns in *trkB* knockout mice (Vitalis *et al.*, 2002).

All of the presently available evidence suggests that whisker-specific neuronal patterns are first established in the PrV, and then transmitted faithfully to the VPM and the barrel cortex. Barrelette patterns fail to form in mice with loss of function mutations in NMDA receptor subunits NR1 and NR2D (Li *et al.*, 1994; Kutsuwada *et al.*, 1996) and in transcription factors *Drg11* (Ding *et al.*, 2003) and *Lmx1-b* (Xiang *et al.*, 2010). So far no link has been identified between NMDA receptors and transcription factors *Drg11* and *Lmx1b*. Several years ago it was noted that transforming growth factor β (TGF- β) family members activin and follistatin play a role in whisker development and patterning in the brainstem. Mice lacking the gene encoding for activin β do not have whiskers and follistatin-deficient mice develop thin and curled whiskers; both strains of mice die within 24 h after birth (Jhaveri *et al.*, 1998). *Activin* βA knockout mice lack barrelettes and the barrelettes are not well developed in follistatin-deficient mice (Jhaveri *et al.*, 1998). A recent study revealed that genetic disruption of TGF- β signaling in TG neurons (by conditional deletion of *Smad4*) results in the absence of or aberrant barrelette patterning in the brainstem trigeminal complex (da Silva *et al.*, 2011). *Smad4* is a nuclear transducer of TGF- β signaling, and TGF- β signaling has been linked to synaptic transmission (Sun *et al.*, 2010) and NMDA receptor-mediated LTP in hippocampus (Müller *et al.*, 2006). Thus, both chemical signaling from the sensory periphery and neural activity mediated through the ION could act cooperatively in setting up the initial scaffolding of barrel patterns two synapses below the neocortex, in the brainstem.

Neural activity and NMDA receptors in plasticity

At all levels of the trigeminal pathway NMDA mediated synaptic activity is recorded as soon as the presynaptic afferents arrive. (Leamey & Ho, 1998; Waite *et al.*, 2000; Khazipov *et al.* 2004). In the newborn rat barrel cortex, thalamocortical inputs generate spindle bursts

in the cortical plate and these are associated with large amplitude NMDA receptor-dependent delta waves (Minlebaev *et al.*, 2009). Thus a physiological substrate is present for Hebbian type synapse consolidation via coactivation of cortical neurons by thalamic cells.

Spatially confined spindle burst activity is a prominent physiological feature of the barrel cortex in newborn rodents (Khazipov *et al.*, 2004; Minlebaev *et al.*, 2007; Yang *et al.*, 2009). These spindle-bursts are driven by glutamatergic synapses involving mainly AMPA/kainate receptors, as well as NMDA receptors and gap junctions and they are compartmentalized by surround GABAergic inhibition (Minlebaev *et al.*, 2007). Peripherally driven activity and postsynaptic NMDAR activation are required for normal development of receptive fields in barrel neurons (Fox *et al.*, 1996; Foeller & Feldman, 2004). LTP at the thalamocortical synapses of the barrel cortex is NMDAR dependent and confined to the first postnatal week, but not restricted to the critical period ending at P3 (Crair & Malenka, 1995). At the thalamocortical synapse LTP results in a switch from slow kainate receptor-mediated synaptic transmission to fast AMPA receptor (AMPA)-mediated transmission during this period (Kidd & Isaac, 1999). Thalamocortical synapses also express NMDA receptor-dependent LTD during development (Feldman *et al.*, 1988). Thus both forms of synaptic plasticity must be in operation during formation and consolidation of barrel patterns initiated by the whisker-specific thalamocortical afferent terminals.

A recent study reported that early gamma oscillations (EGOs) synchronize neurons in a single thalamic barreloid and corresponding cortical barrel during barrel formation in neonatal rats (Minlebaev *et al.*, 2011). It is suggested that sensory inputs from a single whisker lead to activation of gamma oscillator in the corresponding thalamic barreloid, which then imposes topographic feed-forward synchronization in the cortical barrel corresponding to that particular whisker (Minlebaev *et al.*, 2011). In the context of critical period plasticity, EGOs can consolidate coactive inputs via repetitive synchronization of thalamic and cortical neurons, thus creating an activity-dependent competitive environment during pattern formation.

Is there a “molecular switch” which controls the timing of the critical period plasticity in the barrel cortex? This question still awaits an answer. Due to their coincidence detection properties and developmental regulation of their subunit composition NMDA receptors have attracted attention. NMDARs are heteromeric tetramers and each receptor contains the essential NR1 subunit, which binds glycine or D-serine and one or more of the NR2 subunits A–D, which bind glutamate (Wenthold *et al.*, 2003). In the visual cortex, NR2B subunit expression shifts to NR2A subunit expression at the end of the critical period for ocular dominance plasticity (Carmignoto & Vicini, 1992). Dark rearing prolongs developmental NR2B expression and light exposure shifts in favor of NMDA receptors with NR2A subunit (Philpot *et al.*, 2001; Quinlan *et al.*, 1999a,b). There is also a developmental shift from NR2B to NR2A subunits in the thalamocortical segment of the whisker-barrel pathway (Liu *et al.*, 2004), but no such change was found in the PrV at the brainstem level (Lo & Zhao, 2011). Whisker lesion-induced critical period plasticity has been investigated in *NR2A* knockout mice and even though the NMDA current kinetics remained immature, no change was observed in the closure of the critical period (Lu *et al.*, 2001).

In cortex-specific *NR1* knockout (*CxNR1KO*) mice barrels do not develop and the thalamocortical axon terminals show rudimentary patterning only in the region of large mystacial whiskers (Iwasato *et al.*, 2000). In these mice too the duration of the row C whisker induced plasticity, as reflected by the patterning of thalamocortical axon terminals, did not go beyond P4 (Datwani *et al.*, 2002b). Thus, postsynaptic NMDAR function in cortical excitatory neurons does not appear to be essential for thalamocortical axon

plasticity. It remains to be seen whether this plasticity would be affected in thalamus-specific *NR1* knockout mice, although unlikely.

Other key players of hippocampal synaptic plasticity, such as LTP and LTD, have been considered in studies of the barrel cortex critical period plasticity. For example, calcium/calmodulin-dependent kinase II (CaMKII) is an enzyme necessary for LTP and mice mutant for this enzyme lack NMDA receptor-dependent LTP in the barrel cortex (Glazewski *et al.*, 1996; Glazewski *et al.*, 2000; Hardingham *et al.*, 2003). Postsynaptic activation of protein kinase C (PKC) increases synaptic strength and is also involved in LTP in the barrel cortex (Scott *et al.*, 2007). However, none of these molecules have been shown to be essential in governing the timing of the lesion-induced critical period in the barrel cortex.

Glia, perineuronal nets and parvalbumin cells

A role for glial participation in barrel cortex plasticity has also been explored. Oligodendrocytes (OLs) appear in the mouse somatosensory cortex at the end of the critical period (Toda *et al.*, 2008). In this context, critical period plasticity has been investigated in Olig1-deficient and jimpy mouse lines (Toda *et al.*, 2008). In total absence of OLs (Olig1-deficient mice or in jimpy mice), the duration of the critical period is not delayed. Thus, potential involvement of OLs in barrel cortex plasticity is ruled out.

How about astrocytes? In the developing barrel cortex, expression of astrocyte-specific markers, such as the glutamate transporters GLAST and GLT-1 and the glutamine synthetase is confined to the barrel hollows (Voutsinos-Porche *et al.*, 2003; Takasaki *et al.*, 2008). Gap junction proteins, connexins associated with astrocytes (Cx43 and Cx30) also show an elevated expression pattern within the barrel hollows (Houades *et al.*, 2008). Astrocyte-neuron interactions within the barrels are thought to play a major role in whisker-activated information processing in the barrel cortex and various forms of plasticity (reviewed in Giaume *et al.*, 2009). Increased levels of glutamate transporter 1 (GLT1) in astrocytes have been noted during the critical period in the developing barrel cortex (Takasaki *et al.*, 2008). Investigation of row C whisker lesion-induced plasticity in *GLT1* knockout mice did not reveal any change in the duration of the critical period but a significantly lesser degree of plasticity in fusion of the row C barrels and expansion of the neighboring barrels was noted. Diminished lesion-induced plasticity was also observed in astrocyte-specific *glutamate-aspartate transporter (GLAST)* knockout mice (Takasaki *et al.*, 2008). Thus astrocytes might play a role in levels of critical period plasticity by regulating glutamate transporters at the thalamocortical glutamatergic synapses.

An astrocyte-secreted protein thrombospondin promotes synaptogenesis; the neuronal thrombospondin receptor involved in synapse formation has been identified as alpha2delta-1, also the receptor for the anti-epileptic drug gabapentin (Eroglu *et al.*, 2009). Gabapentin antagonizes thrombospondin binding to alpha2delta-1 and inhibits synapse formation. Examination of the whisker row C lesion induced plasticity in the barrel cortex of mice given gabapentin injections between P0-7 or in *TSP1/2* double knockout mice revealed exaggerated plasticity and expansion of intact barrels but did not affect the timing of this response confined to the critical period (Eroglu *et al.*, 2009).

Perineuronal nets formed by chondroitin sulfate proteoglycan aggregates, parvalbumin-positive GABAergic neurons and embryonic homeoprotein, Otx2, reportedly regulate the timing of the critical period for ocular dominance plasticity in the visual cortex (Pizzorusso *et al.*, 2002; Sugiyama *et al.*, 2008). A similar role for proteoglycan aggrecan and parvalbumin-positive neurons has been implicated for the barrel cortex plasticity following whisker trimming (McRae *et al.*, 2007). The density of parvalbumin-positive cells and perineuronal nets was investigated in adolescent mouse barrel cortex and following removal

of all but one whisker (univibrissa rearing or single whisker experience) on the snout or removal of every second whisker (chessboard deprivation) (Nowicka *et al.*, 2009). Univibrissa rearing, but not chessboard deprivation, increased the density of perineuronal nets and parvalbumin-positive cells in the deprived barrels (Nowicka *et al.*, 2009). These data suggest the involvement of parvalbumin-positive GABAergic neurons and perineuronal proteoglycan nets in plasticity of the barrel cortex in adolescent and adult mice as discussed in the next section.

Is the timing of the lesion-induced critical period plasticity set in subcortical structures?

In one of the pioneering studies (Durham and Woolsey, 1984) the timing of the critical period closure was reported to follow a succession from the brainstem to the barrel cortex between P0-P5. The only evidence strongly pointing to the subcortical regulation of critical period plasticity comes from studies involving excess serotonin in the barrel cortex. Pharmacological manipulations by administering MAOA inhibitor clorgyline in neonatal rats delay barrel formation with no apparent effects on the termination of the critical period by P4 (Boylan *et al.*, 2001). As described earlier, in *Maoa* knockout mice thalamocortical axons do not segregate and the barrels do not form (Cases *et al.*, 1996). When these mice are treated daily with parachlorophenylalanine (PCPA, an inhibitor of tryptophan hydroxylase that significantly lowers 5-HT levels), barrels form much later during development. When neonatal row C whisker lesions were performed in *Maoa* knockout mice with delayed barrel formation the end of the critical period plasticity (P3) did not shift to a later age, suggesting that the timing of the critical period is not set in the cortex (Rebsam *et al.*, 2005). Thus, critical period plasticity responses of thalamocortical axons and their postsynaptic partners in the barrel cortex may be a simple transfer of plasticity effects coming from the subcortical trigeminal centers.

Multiplicity of barrel cortex plasticity

Whisker follicle or ION lesions are not the only experimental manipulations used in studying barrel cortex plasticity. Whisker pairing (clipping of all whiskers but two), univibrissa rearing (single whisker experience or trimming all whiskers except one), sparing of one row of whiskers and clipping all the others, or chessboard whisker deprivation have been used as forms of noninvasive sensory deprivation. These studies are more comparable to monocular lid suture or dark rearing experiments performed in the visual system research.

Peripheral manipulations without follicle or nerve damage do not yield robust structural defects in the organization of whisker patterns in the brain and the effects are not strictly confined to perturbations done during the first few days after birth (Simons & Land, 1987; Fox, 1992). In fact, sensory experience-dependent plasticity has been noted throughout the life of a rodent (Armstrong-James *et al.*, 1994; Fox, 1992, 1994, 2002; Isaac *et al.*, 1997; Lebedev *et al.*, 2000; Maier *et al.*, 2003; Rema *et al.*, 2003). For example, whisker trimming in juvenile rats leads to long-lasting receptive field enlargement in the barrel cortex (Simons & Land, 1987). Poor rough surface discrimination is another consequence of bilateral whisker trimming from birth to 45 days of age (Carvell & Simons, 1996). Bilateral whisker trimming during the lesion-induced critical period leads to profound behavioral deficits later in life (Lee *et al.*, 2010). P0-P3 whisker-trimmed adolescent rats display poor performance in a gap crossing test, increased locomotion in an open-field test and increased investigative and contact behaviors in a social interaction test (Lee *et al.*, 2010). These results indicate that sensory experience is critical during the formative period of the barrels (P0-3) for behavioral development as well.

Layers II/III (supragranular) neurons receive inputs from the barrel cells and they too are susceptible to alterations of sensory inputs during development (Fox, 1992, 2002; Diamond *et al.*, 1994; Glazewski & Fox, 1996). The timing of layers II/III critical period is not as well defined as the one for peripheral lesion-induced structural plasticity of the layer IV; it varies depending on the study but it is usually confined to the second and third postnatal weeks.

Alteration of sensory input by all but one whisker experience during development leads to plasticity effects in the strength of layer IV to layers II/III and intra layers II/III horizontal connections but with different timing; layer IV to II/III synapses show an earlier and shorter critical period between P10-14 (Lendvai *et al.*, 2000; Stern *et al.*, 2001; Maravall *et al.*, 2004a, b; Shoykhet *et al.*, 2005). A longer and later critical period window has been determined for the horizontal connections between layer II/III neurons (Wen & Barth, 2011).

Among the forms of plasticity seen in layer II/III is alterations in axonal projection fields of horizontal connections. Removing all but one whisker after the first postnatal week has significant plasticity effects in layers II/III indicating increased lateral transmission from the barrel corresponding to the experienced single whisker and failure of vertical transmission from deprived barrels (Fox, 1992). Pairing of whisker rows (i.e., trimming of all whiskers except those in select rows) during postnatal development (P7-15) also lead to increased horizontal projections from one spared row column to neighboring spared row columns and decreased horizontal projections from spared row columns to neighboring deprived row columns in supragranular layers (Broser *et al.*, 2008). Thus, during the critical period for layers II/III horizontal corticocortical connections are susceptible to peripherally driven sensory experience.

Molecular mechanisms of layer II/III plasticity have received little attention. One study reported that type I cannabinoid (CB1) receptors are involved in mediating whisker representation and critical period plasticity in layer II/III of the rat barrel cortex (Li *et al.*, 2009). Pharmacological blockade of CB1 receptors during the early critical period for layer II/III (P12-16) disrupted functional whisker map development, led to impaired whisker tuning and prevented experience-dependent plasticity. Blockade after P25 did not affect whisker tuning or expression of experience-dependent plasticity.

Defects in synaptic plasticity that follow learning rules have been linked to cognitive impairments. One such condition is the fragile X syndrome caused by mutations in the *Fmr1* gene. *Fmr1* knockout mice have been used to model this cognitive impairment syndrome. In the absence of fragile X mental retardation protein (FMRP) development of cortical glutamatergic synaptic transmission is impaired with persistence of silent synapses and the plasticity window is delayed in the barrel cortex (Harlow *et al.*, 2010). More strikingly, plasticity in layers II/III was disrupted: strength of layer IV inputs was reduced and did not show experience-dependent plasticity (Bureau *et al.*, 2008).

Concluding Remarks

The mouse barrel cortex has become an excellent model system to study cortical plasticity. Developmental studies have begun unraveling a complex genetic programming that directs areal specification of the neocortex. Numerous axon guidance molecules have been identified in wiring of the thalamus and neocortex. The roles of sensory activity and experience in shaping somatosensory cortical map and patterning of neural elements within the map have been underscored. Intracellular signaling pathways downstream from glutamatergic synaptic transmission are emerging. Various forms of developmental plasticity and layer-specific critical periods have been identified. Barrel cortex is also emerging as a model to investigate synaptic malfunction in developmental cognitive

disorders. We do not yet know the molecular mechanisms underlying the critical period for structural plasticity of the barrel cortex and how the duration of this period is determined, even though the available evidence suggests that the timing of the critical period might be set in subcortical structures. Future studies aimed at identifying differential gene expression before, during and at the closure of the critical period at various levels of the trigeminal pathway will undoubtedly shed light on these questions.

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Abbreviations

AC1	Adenylyl cyclase type I
AMPA	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor or quisqualate receptor
BDNF	brain-derived neurotrophic factor
CB1	type 1 cannabinoid receptors
CaMKII	calcium/calmodulin-dependent kinase II
E	embryonic day
EGOs	early gamma oscillations
FGF8	fibroblast growth factor 8
FMRP	fragile X mental retardation protein
GAP-43	growth-associated phosphoprotein
GLAST	astrocyte-specific glutamate-aspartate transporter
GLT1	glutamate transporter 1
ION	Infraorbital branch of the trigeminal nerve
LTP	long-term potentiation
LTD	long-term depression
mGluR5	metabotropic glutamate receptor 5
MAOA	monoamine oxidase A
NGF	Nerve growth factor
NT-3	neurotrophin-3
NMDA	N-methyl-D-Aspartate
OIs	Oligodendrocytes
P	postnatal day
PCA	p-chloroamphetamine
PCPA	parachlorophenylalanine
PLC β	phospholipase C- β

PKC	protein kinase C
POm	posteromedial nucleus
PrV	Principal sensory nucleus of the trigeminal nerve
RIM	RAB interacting molecule, a protein controlling synaptic vesicle release
SHH	sonic hedgehog
SP	Subplate
5-HT	serotonin
TCA	Thalamocortical axon
TG	Trigeminal ganglion
TGF-β	transforming growth factor β
TSP	Thrombospondin
TTX	Tetrodotoxin, a Na ⁺ channel blocker
VPM	Ventroposteromedial nucleus of the thalamus
VPL	Ventroposterolateral nucleus of the thalamus
WNT	Drosophila wingless
WP	Whisker pad

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Figure 2.

Schematic diagram illustrating the classical structural plasticity in the barrel cortex following row C whisker lesions or infraorbital nerve transection. These effects are only seen when peripheral lesions are performed up to postnatal day 3. The patterns and deficits are routinely assessed by histochemical stains such as succinic dehydrogenase or cytochrome oxidase histochemistry or with immunohistochemistry for TCA markers such as 5-HTT or vesicular glutamate transporter 2 or by Nissl or Golgi stains for neuronal and dendritic organization.

Table 1

Chronology of events during development of the mouse whisker-barrel pathway

E9	Neurogenesis in the trigeminal ganglion from E8.5 to E13 (Davies & Lumsden, 1984; Wilkinson <i>et al.</i> , 1996; Erzurumlu <i>et al.</i> , 2010)
E10	E10 (30-somite-stage) A few pioneer axons of the ophthalmic branch of the trigeminal nerve reach past the eyecup, maxillary fibers begin target directed elongation; they are about 100 μ m away from the maxillary process (the site of the whisker pad) (Stainier & Gilbert, 1990). E10.5 (37-somite-stage) The pioneering maxillary (infraorbital nerve) axons reach the maxillary epithelium (presumptive whisker pad) and begin branching (Stainier & Gilbert, 1990). Central TG axons bifurcate upon entering the pontine flexure and each branch elongates to form the rostral (ascending) and caudal (descending) trigeminal tract. (Inferred from E12 rat data, Erzurumlu & Jhaveri, 1992b; see also Ding <i>et al.</i> , 2003 for the mouse). The PrV cells emerge from the ventricular zone of the ventral aspect of the hindbrain around E10.5 and they express transcription factor Drg11 (Ding <i>et al.</i> , 2003).
E11	PrV cell axons cross the midline as soon as they are born (E10, E11) (Kivrak & Erzurumlu, 2012) and their midline crossing is guided by cooperative action of netrin-1 and slit proteins (Mirza <i>et al.</i> , 2012). E11.5 Drg11-expressing PrV cells migrate ventrolaterally toward the region adjacent to the TG (Ding <i>et al.</i> , 2003). E10.5-14.5 Neurogenesis in the dorsal thalamus (Wang <i>et al.</i> , 2011)
E12	Whisker follicles begin developing along five rows of skin ridges of a plate of thickened ectoderm (whisker pad) at E12. Individual follicles develop in a caudal to rostral sequence. A small nerve plexus is formed under the skin ridge and a dermal condensation occurs just above it; the epithelium over the dermal condensation thickens and grows down into the dermal condensation forming the follicle. (Yamakado & Yohro, 1979; Van Exan & Hardy, 1980). A gross topographic order in trigeminal projections to the whisker pad and the brainstem is present from the onset (Ding <i>et al.</i> , 2003; Da Silva <i>et al.</i> , 2011)
E13	TCAs from the VPM arrive at the diencephalon-telencephalon boundary and by E13.5 pass through a permissive “corridor” en route to the neocortex (Lopez-Bendito & Molnar, 2003; Price <i>et al.</i> , 2006; Lopez-Bendito <i>et al.</i> , 2006).
E14	E14 Central TG axons emit radially oriented collaterals into the brainstem trigeminal nuclei (Ding <i>et al.</i> , 2003). E14-E15 Layer IV neurons are born in the somatosensory cortex (Angevine & Sidman, 1961; Rebsam <i>et al.</i> , 2002)
E15	PrV is fully formed and central TG axons begin their arborization phase in the brainstem trigeminal nuclei (Ding <i>et al.</i> , 2003; Erzurumlu <i>et al.</i> , 2010) E15 PrV axons arrive in the midbrain (Erzurumlu & Kivrak, 2012) Pioneering TCAs reach the prospective somatosensory cortex (Molnar <i>et al.</i> , 2003)
E16	VPM axons extend along the internal capsule.
E17	E17 PrV axons reach the VPM (Ding <i>et al.</i> , 2003; Kivrak & Erzurumlu, 2012)
E18	E 18.5 central TG axons begin forming whisker-specific clustered terminal fields (Ding <i>et al.</i> , 2003) E18-P0 PrV axons form bands (rows) in the VPM following an initially diffuse and exuberant invasion of the VPM (Kivrak & Erzurumlu, 2012)
E19-P0	P0-P1 Barrelette patterns emerge in the PrV (Ma, 1984; Li <i>et al.</i> , 1994). TCAs arrive in the cortical plate (Senft & Woolsey, 1991; Agmon <i>et al.</i> , 1993; Rebsam <i>et al.</i> , 2002)
P1	PrV axons form bands in VPM (Kivrak & Erzurumlu, 2012)
P2	P2 patches within bands appear in VPM (Kivrak & Erzurumlu, 2012) TCA terminals form barrel rows in S1 cortex (Rebsam <i>et al.</i> , 2002)
P3	P3 Barreloids are visible in the VPM (Durham & Woolsey, 1984; Kivrak & Erzurumlu, 2012) Whisker-specific TCA terminal patches appear within barrel rows (Rebsam <i>et al.</i> , 2002; Lee <i>et al.</i> , 2005a) P3-P4 end of critical period for structural plasticity following whisker follicle or ION damage (Durham & Woolsey, 1984; Datwani <i>et al.</i> , 2002b; Rebsam <i>et al.</i> , 2005) Closure for critical period plasticity for bilateral whisker trimming (Lee <i>et al.</i> , 2009).
P4	End of critical period for structural plasticity
P5	P5-P7 Barrels as cellular aggregates become distinct (Rice <i>et al.</i> , 1985)
P6	Polarized dendritic orientation of barrel cells become apparent (Espinosa <i>et al.</i> , 2009).
P7	
P8	
P9	
P10	P10-P14 Critical period plasticity for layer IV to II/III synapses (Single whisker experience-induced synaptic strength; Lendvai <i>et al.</i> , 2000; Stern <i>et al.</i> , 2001; Maravall <i>et al.</i> , 2004a, b; Shokhet <i>et al.</i> , 2005).

P11	
P12	
P13	P13-P16 Critical period for horizontal connections between layer II/III neurons (Single whisker experience-induced synaptic strength; Wen & Barth, 2011)
P14	Eyes open, active whisking starts (Landers & Ziegler, 2006) End of critical period for layer IV to II/III synapses.
P15	
P16	End of critical period for horizontal connections between layer II/III neurons.
P17	