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Impact of Thalamocortical Input on Barrel Cortex Development

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Abstract

The development of cortical maps requires the balanced interaction between genetically determined programs and input/activity-dependent signals generated spontaneously or triggered from the environment. The somatosensory pathway of mice provides an excellent scenario to study cortical map development because of its highly organized cytoarchitecture, known as the barrel field. This precise organization makes evident even small alterations in the cortical map layout. In this review, we will specially focus on the thalamic factors that control barrel field development. We will summarize the role of thalamic input integration and identity, neurotransmission and spontaneous activity in cortical map formation and early cross-modal plasticity.

Keywords

Thalamus; spontaneous activity; somatosensory system; cortical maps; calcium waves; plasticity

Introduction

Sensory information flows from peripheral receptors to cortical structures through a sequence of precisely organized projections. Before reaching primary sensory cortices, topographically organized sensory afferents cluster in modality-specific thalamic nuclei. Subsequently, each thalamic nucleus conveys sensory information to its corresponding cortical region preserving topographical organization (Petersen, 2007; Huberman *et al.*, 2008; Tsukano *et al.*, 2017). This means that besides the message encoded by patterns of action potentials, the specific cortical site where synaptic transmission takes place enriches the neural message with precise positional information, highlighting the relevance of fine-scale connectivity.

Highly elaborated neural networks rely on precise wiring during development. In rodents, the thalamocortical circuits' assembly starts embryonically and finishes a few days after birth (Jhaveri *et al.*, 1991; Schlaggar & O'Leary, 1994). During this period, the thalamocortical ensemble experiences elongation and branching of projections, synaptogenesis, synaptic deletion, refinement and local synaptic connections. Numerous

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investigations have provided compelling evidences that intrinsic and extrinsic mechanisms act together to achieve modality-specific and highly organized thalamocortical connections (Hanganu-Opatz, 2010). In particular, the rodent somatosensory system emerged as a helpful model to elucidate connectivity principles due to the unique one-to-one relationship between facial whiskers on the snout and barrel-like modules in layer 4 (L4) of the contralateral primary somatosensory cortex (S1) (Woolsey & Van der Loos, 1970).

Development of the thalamocortical somatosensory system

The topographic map found at every level along the somatosensory system recapitulates the whisker layout on the snout. Each whisker has a specific representation in the ipsilateral principal trigeminal nucleus of the brainstem (PrV), named barrelette (Ma & Woosley, 1984); in the contralateral ventro-posteromedial nucleus of the thalamus (VPM), named barreloid (van der Loos, 1976); and in the contralateral somatosensory cortex (S1), named barrel (Van der Loos & Woolsey, 1973). Every station develops following the same temporal sequence. First, the afferent terminals cluster delineating barrel-like structures. And then, the postsynaptic cells at the brainstem, thalamus and cortex aggregate and refine their dendritic trees in order to overlap the initial presynaptic clusters. Combining both pre- and postsynaptic processes, whisker-related modules arise and the topographical map becomes evident.

In mice, the axons from the PrV project to the thalamus (Erzurumlu *et al.*, 1980), crossing the midline around embryonic day (E)11.5 elongating rostrally towards the contralateral thalamus. These axons reach the VPM around E17.5; they arborize and finally refine forming barreloids during the first postnatal week (Kivrak & Erzurumlu, 2012). Before the trigemino-thalamic axons reach the thalamus, the thalamocortical axons (TCAs) have already started to project to the cortex, independently of the peripheral input (López-Bendito & Molnár, 2003). The extension of the TCAs to the cortex is controlled by the expression of thalamic and subpallial molecular guidance cues, independently of the cortex. Adhesion molecules, guidance cues and guidepost cells, guide TCAs towards the cortex with a highly coordinated topographical pattern (Molnar *et al.*, 1998; Braisted *et al.*, 1999; Molnar *et al.*, 2012; Leyva-Díaz & Lopez Bendito, 2013; Garel & Lopez-Bendito, 2014). Some of these important molecules are Semaphorins/Plexin, Ephrins/Eph, Netrins/DCC and others that are essential for a proper development of the TCAs. Moreover, recent studies have shown that spontaneous calcium activity controls, at least in part, TCAs development by means of transcriptional regulation of critical molecules such as *Robo1, Slit1* and *DCC* (Mire *et al.*, 2012; Castillo-Paterna *et al.*, 2015). These results suggest that spontaneous activity intrinsically modulates the rate of axon extension in the thalamocortical system.

Thalamocortical cells start to extend their axons ventrally from the diencephalon to turn laterally crossing the boundary between the diencephalon and the telencephalon at E12.5. At E13.5, they navigate within the internal capsule (IC) and corridor cells (López-Bendito *et al.*, 2006; Uemura *et al.*, 2007) to arrive to the pallial-subpallial boundary (PSPB) at the entrance of the cortex. Corticothalamic axons (CTAs) leave the cortical plate around the same time and meet the TCAs at the PSPB around E14.5 (Jacobs *et al.*, 2007; Deck *et al.*, 2013; Mandai *et al.*, 2014). Before the neurons from the primary cortical areas are born, the

TCAs wait in the subplate region a few days in their specific sensory modality cortex until they enter in their proper cortical layer (López-Bendito & Molnár, 2003). During this period, TCAs transiently connect with subplate neurons and this communication seems to be crucial for the later topographic innervation of the cortical plate (Catalano & Shatz, 1998; Higashi *et al.*, 2002; Hull *et al.*, 2009; Kanold & Luhmann, 2010; Bagnall *et al.*, 2011; Constantinople & Bruno, 2013). The neurites of subplate neurons undergo many processes of remodeling, from a wide pattern reaching the marginal zone to confined localizations in prospective barrel hollows, barrel septa or below L4 (Pinon *et al.*, 2009). As subplate neurons are electrically mature (Luhmann *et al.*, 2003), they could function as an effective bridge between immature thalamic inputs and cortical targets.

Although the extension of the TCAs to the cortex is independent of mechanisms underlying cortical regionalization, intrinsic signals from the cortex are involved in the formation of the final barrel map. Early manipulations of specific genes *(Fgf8* and *Pax6)* cause an abnormal organization of TCAs in the telencephalon, indicating that they use intracortical positional information as well (Fukuchi-Shimogori & Grove, 2003; Shimogori & Grove, 2005; Zembrzycki *et al.*, 2013). Moreover, in animal models that lack transcription factors important for normal arealization of the cortex such as *Coup-TF1*, *Emx1* or *Emx2*, TCAs are able to reach their proper S1 target area and form the barrel map (Hamasaki *et al.*, 2004; Armentano *et al.*, 2007; Stocker & O'Leary, 2016). Interestingly, TCAs are topographically pre-ordered in the subpallium and this organization seems to be crucial for the development of cortical features. In a relevant study, it was shown that if the topographical positioning of somatosensory TCAs is altered, the barrel map is not formed in S1 (Lokmane *et al.*, 2013). Thus, revealing that sensory map transfer relies on preordering of axons along their trajectory. Therefore, altogether these studies indicate that although TCAs organization in the subpallium is independent of normal cortical arealization, it can severely affect the later formation of the barrel map. Cortical intrinsic information also contributes to the final positioning of TCAs in S1.

The formation of barrels in L4 of S1 comprises two main events. First, immediately after birth, TCAs from VPM are pruned in the cortex giving rise to clusters that delineate the barrel territory. Collaterals that are not confined to a single barrel are eliminated (Rice et al., 1985). Second, L4 spiny stellate neurons surround thalamic axonal clusters to form barrel walls (Killackey, 1973; Woolsey et al., 1975; Simons & Woolsey, 1984; Jensen & Killackey, 1987; Agmon et al., 1995). By postnatal day (P) 4, barrels are evident and each of them receives innervation from a single barreloid (Agmon et al., 1995).

Thalamocortical communication shapes the barrel map

In every relay station throughout the whisker-barrel pathway, afferents imprint their spatial organization to the postsynaptic target (Killackey *et al.*, 1995; Sehara & Kawasaki, 2011). In particular, the thalamocortical projection to L4 has been an experimentally accessible system for understanding the mechanisms involved in the precise formation of circuits in S1. A large body of work indicates that mechanisms dependent on spontaneous and periphery-driven neural activity operate to transmit topological information sequentially from afferents to target neurons.

Spontaneous activity during the early ontogenetic stages regulates, among others, the following physiological processes: neurogenesis, neuronal identity acquisition, cell migration, gene expression, axonal and dendritic projections, growth and differentiation, formation and refinement of topographic maps (Spitzer, 2006; Luhmann, 2017). In sensory systems, correlated spontaneous activity promotes functional maturation of intracortical and thalamocortical circuits (Cang *et al.*, 2005; Hanganu-Opatz, 2010; Ackman & Crair, 2014).

Although the origin and propagation mechanisms of spontaneous correlated activity are still unclear, these activity patterns are transmitted through different structures before sensory onset. In the visual system, retinal waves of newborn rats robustly correlate with spindle burst activity in the contralateral primary visual cortex (V1); however, a large fraction of cortical activity persists when retinal waves are absent suggesting that circuits intrinsic to the brain might be operating to generate early coordinated activity (Hanganu *et al.*, 2006; Colonnese & Khazipov, 2010). In the somatosensory system, while peripheral inputs drive spindle bursts and gamma oscillations in the barrel cortex of newborn rodents, disconnecting peripheral pathways reduces but does not abolish thalamic and cortical activity (Khazipov *et al.*, 2004; Minlebaev *et al.*, 2011; Yang *et al.*, 2013). It is not clear how thalamic and cortical neurons communicate during early stages; an increasing number of publications suggest that subplate neurons are implicated in the generation of cortical oscillatory patterns (Molnár *et al.*, 2003; Kanold & Luhmann, 2010; Hoerder-Suabedissen & Molnar, 2015). Overall, these results suggest an effective vertical communication between developing subcortical and cortical stations even before dedicated sensory processing. In this way, spontaneous electrical activity might function as a messenger carrying topographic information and, therefore, facilitating the formation of sensory maps. The following paragraphs will sum up the current knowledge regarding thalamocortical pre-and postsynaptic elements involved, in an activity-dependent manner, in barrel cortex organization.

Any manipulation to tackle map formation must be done before barrels become apparent in the cortex. In rodents, this sensitive window ends between P3 and P5 (Rice & Van der Loos, 1977; Rice *et al.*, 1985). Indeed, seminal studies demonstrate that short-cutting peripheral input within a few days after birth, by means of infraorbital nerve injury (ION) or damage to the mystacial vibrissae, impairs thalamic afferents clustering and, consequently, L4 cells do not aggregate into barrels (Van der Loos & Woolsey, 1973; Weller & Johnson, 1975; Killackey *et al.*, 1976). Later manipulations did not produce map defects (Woolsey & Wann, 1976) providing strong evidence that an intact periphery, before barrel pattern becomes visible, is an essential condition for a development of a normal map. However, these experiments could not rule out whether the relevant factor for barrel map formation is the presence of the peripheral input or the neural activity that flows through them.

Inspired by results from the visual system (Stryker & Harris, 1986), the idea that neural activity influences barrel formation was tested using pharmacological blockade of cortical NMDA receptors (NMDAR). In these studies, local and systemic inhibition triggered functional and morphological disorders in the barrel map (Fox *et al.*, 1996; Mitrovic *et al.*, 1996). Despite that several lines of evidence supported these results, other reports led to contradictory conclusions (Chiaia *et al.*, 1992; Henderson *et al.*, 1992; Schlaggar *et al.*, 1993). The forthcoming molecular genetics strategies in mice overcome pharmacological

data inconsistency demonstrating that targeted deletion of genes related to neural activity induced defects on the whisker representation along the somatosensory pathway (Erzurumlu & Kind, 2001; Wu *et al.*, 2011; Erzurumlu & Gaspar, 2012). Furthermore, this targeted gene deletion allows a comprehensive molecular dissection of the barrel map formation, with the added possibility of spatial and/or temporal control.

Initial approaches using transgenic mice consisted in the ablation of a gene from the whole organism. With this strategy, many null mice were generated for genes involved in presynaptic neurotransmitter release and modulation, and also in postsynaptic activity and signaling. Global knockout of genes related to synaptic function such as adenylyl cyclase 1 (AC1), NMDA receptor subunit 1, metabotropic glutamate receptor 5, phospholipase C-beta1, cAMP-dependent protein kinase type II regulatory subunit, monoamine oxidase A or sodium-dependent 5-HT transporter showed phenotypes with aberrant barrel map organization (Li *et al.*, 1994; Cases *et al.*, 1996; Welker *et al.*, 1996; Iwasato *et al.*, 1997; Abdel-Majid *et al.*, 1998; Hannan *et al.*, 2001; Persico *et al.*, 2001; Salichon *et al.*, 2001; Lu *et al.*, 2003; Rudhard *et al.*, 2003; Gheorghita *et al.*, 2006; Inan *et al.*, 2006; Lu *et al.*, 2006; Watson *et al.*, 2006; Wijetunge *et al.*, 2008; She *et al.*, 2009). Altogether, these studies identified genes required for barrel map formation. However, these findings could not be ascribed to specific effects on the neocortex, as subcortical aberrant maps are more than likely sequentially transmitted to the cortex. A direct assessment of how thalamocortical communication affects barrel formation required site-specific deletions in the thalamus or the cortex.

Selective loss-of-function models confine the deletion of a gene to a specific tissue or group of cells (Figure 1). The cortical knockout mice for the NR1 subunit of the NMDAR showed defective thalamocortical neurotransmission (Iwasato *et al.*, 2000; Datwani *et al.*, 2002). In this model, upstream subcortical stations, cortical layers and somatotopy develop normally; but, in the barrel cortex, thalamocortical afferents form rudimentary patches, L4 cells fail to locate around barrel edges and their dendritic field does not orientate towards barrel hollows as in wild type mice. Single axon analyses in these mutant mice revealed that thalamocortical afferents span through larger territories than wild type axons (Lee *et al.*, 2005). A similar aberrant barrel map phenotype is found in another model with defective glutamatergic transmission between thalamocortical innervations and L4 cells. Cortex-specific metabotropic glutamate receptor 5 (mGluR5) knockout mice also exhibit abnormal TCA patterning, as well as L4 cells with cell bodies evenly distributed and symmetric dendrites (Ballester-Rosado *et al.*, 2010). While these studies suggest a pivotal role of postsynaptic glutamatergic receptors in barrel map formation, it is unclear whether postsynaptic defects, such as cell body misplacement or lack of dendritic polarization, reflect a cell-autonomous requirement or they are inherited defects from the presynaptic site due to the abnormal distribution of TCAs.

A cell-autonomous function of a gene might be assessed in mosaic models in which only a subpopulation of cells carries the deletion. In this way, mutant cells reside in a wild type environment. Loss of the NR1 or NR2B subunit of NMDARs or mGluR5 in a subset of L4 neurons revealed that postsynaptic defects have, partly, a cell-autonomous regulation in S1(Espinosa *et al.*, 2009; Mizuno *et al.*, 2014; Ballester-Rosado *et al.*, 2016). In these mosaic

animals, as expected, L4 wild type spiny stellate cells are localized at barrels edges and develop asymmetric dendrites biased towards barrel hollows. Mutant neurons display, on one hand, cell bodies properly aligned to barrel walls in most of the cases (except in mGluR5 mosaic animals; NR1 KO cells seem normal although there is not a direct quantification); and on the other hand, abnormal symmetric dendrites without barrel preference. Same results are found in mice that lack AC1 in the cortex (Iwasato *et al.*, 2008). AC1 participates in the downstream signaling triggered by NMDAR activation. Notably, the same phenotype is observed if L4 neural activity is silenced instead of interfering with glutamatergic transmission, cell body allocation develops properly but the biased arborisation pattern is altered (Egusa *et al.*, 2016). Despite the fact that relevant molecules have been identified, the mechanism of dendritic refinement remains unclear. One possible approach might be chronic calcium imaging experiments over L4 spiny stellate dendrites during the refinement process both in wild type and mutant cells *in vivo.*

Non-cell autonomous effects indicate that extrinsic factors partly instruct barrel formation. Indeed, perturbations in the presynaptic side, the TCAs, cause even more severe disruptions of barrel map organization. These perturbations end up in nearly abolished or reduced (severity depends on the approach) neurotransmitter release, suggesting a key role of activity-dependent mechanisms. For instance, elimination of vesicular glutamate transporters type 1 and 2 from somatosensory nuclei, nearly prevents neurotransmission. In these mice, thalamic afferents fail to cluster into whisker related patches, L4 spiny stellate characteristic morphology is absent and cortical cytoarchitecture does not emerge (Li *et al.*, 2013). Thus, in addition to recapitulate the cortical phenotype shown by the aforementioned studies in which neurotransmission was disrupted by targeting the postsynaptic glutamate receptors, this model showed dramatic defects on the thalamic afferents too. If neurotransmission is partly affected rather than almost completely blocked, thalamic afferents do cluster, albeit immature, and only the defective cortical phenotype develops strongly. This is the case for the thalamic conditional ablation of Rab3 interacting molecules (RIM) isoforms, components of the synaptic release machinery (Narboux-Neme *et al.*, 2012). Also, the conditional ablation of thalamic AC1 (Suzuki *et al.*, 2015), a molecule that in the presynaptic compartment might regulate glutamate release, shows a stronger cortical phenotype in comparison to thalamic defects –in these mice TCAs clusters are less defined than in the RIM ablation model. These perturbations further support a key role for neurotransmission-mediated mechanisms on barrel map organization.

Thalamic input shapes cortical area identity

The above-mentioned results clearly support a central role of neural activity on barrel map formation. Work in recent years has deepened the knowledge about the function of the thalamus in the development of the somatosensory system, not only in setting the map, but also in influencing the identity of successive relay stations. Sensory pathways are organized in a stereotyped way where the peripheral input contacts a first-order (FO) thalamic nucleus that in turn projects to the corresponding primary sensory cortical area. The output from the primary sensory area projects back to a higher-order (HO) thalamic nucleus that projects to secondary sensory cortical areas. Recent studies suggest that the nature of the input to a

territory exerts a strong influence over the postsynaptic molecular and functional differentiation.

Taking advantage of a genetic model of postnatal ablation of the VPM, the FO somatosensory thalamic nucleus, it was shown that the attributes of the L4 thalamorecipient cells in S1 are tightly controlled by the nature of the subcortical input (Pouchelon *et al.*, 2014). In the absence of a VPM input to S1, the posteromedial nucleus (POm), a HO somatosensory nucleus, takes over and acts as the main thalamic driver for L4 cells of S1 (S1L4). Remarkably, in this model S1L4 cells show a genetic differentiation program similar to the one of L4 neurons of secondary areas (S2L4). Moreover, the connectivity and functional properties of S1L4 neurons resemble those of S2L4 neurons. Re-specified L4 neurons respond to both haptic and noxious stimuli, in contrast to the segregation of these sensory modalities in different cortical circuits that occur in normal conditions. Also, barrels are missing in the re-specified S1, and the stimulation of a single whisker leads to a diffuse activation of the immediate–early gene c-fos in S1L4, rather than to the activation of the corresponding barrel. It is interesting to note that in the visual system, the thalamocortical input also drives the differentiation of patterned gene expression that distinguishes primary and HO visual areas (Chou *et al.*, 2013), suggesting that the control of cortical layer properties by the nature of the input may be extensive to other sensory modalities.

The instrumental role of the input in defining target identity is extensive to subcortical stations, such as the thalamus. By means of a transcriptional analysis to compare gene expression of FO and HO thalamic nuclei, it was found that hierarchical order (i.e. first/higher order relationship) rather than the modality of the stimulus is the determinant factor for sharing a similar transcriptional program (Frangeul *et al.*, 2016). HO (LP and POm) and FO (dLGN and VPM) nuclei are segregated in respective groups. The same applies, with less astringency, to the auditory thalamic nuclei. These transcriptional programs are determined by the input from the periphery. Interestingly, in the absence of external inputs, FO thalamic nuclei become HO nuclei or, in other words, HO-type genetic identity is a ground state property from which FO features emerge in the presence of a peripheral input.

The results obtained with the genetic model of postnatal ablation of the VPM (Pouchelon *et al.*, 2014) are consistent with the effect of early ION ablation (Frangeul *et al.*, 2016), as in both paradigms the somatosensory thalamus is rendered to a HO-like identity. This is also convergent to the results obtained in the visual system (Grant *et al.*, 2016). In enucleated animals, corticothalamic L5 neurons aberrantly innervate the (modified) dLGN. Interestingly, blocking the spontaneous activity of the retina with epibatidine leads to similar changes in the pattern of corticothalamic connectivity. This indicates that activity feeds a forward mechanism that controls the identity (or bias the identity) towards a FO in the presence of activity or towards a HO in its absence.

Cross-Modal plasticity affecting the somatosensory cortex: Role of thalamic waves

The plasticity that takes place in the brain represents an adaptive response of neural networks to patterns of stimuli. It is known that patterned neural activity is able to alter the

connectivity and the specificity of cortical areas. As aforementioned, a paradigm extensively used to unravel the role of the afferent input and their electrical properties in the development of the cortex, is the deprivation of one sensory modality. The deprivation of a sensory input leads to striking effects on the development of the remaining modalities, and furthermore, an adaptive reorganization of the deprived neurons that integrate a new function. This neuroplastic phenomenon is called “cross-modal plasticity”. The characterization of the functional rearrangement that takes place in the sensory systems after sensory deprivation may help to understand the role of intrinsic and extrinsic mechanisms involved in cortical development.

The classical view of cross-modal plasticity claims that the neural changes observed in the cortical areas of sensory-deprived rodents are due to the increased experience-dependent neuronal activity of the intact sensory system during postnatal life. Studies in rats enucleated at birth, have demonstrated that there is a recruitment of the rostral part of visual cortex from the primary somatosensory cortex, with the consequent higher whisker responsiveness and improved exploring skills (Toldi *et al.*, 1994; Toldi *et al.*, 1996). Moreover, these deprived rats have longer whiskers (Rauschecker *et al.*, 1992) and an increment in the experience-driven activity along the trigeminal pathway (Bronchti *et al.*, 1992; Zheng & Purves, 1995).

While the finding of an experience driven mechanism for cross-modal plasticity was groundbreaking, it was unable to explain the early adaptations found before or soon after the onset of sensory experience. Recent studies, strongly point to the existence of experience-independent mechanisms (Mezzera & Lopez-Bendito, 2015). For example, in mice, enucleations at birth change the expression pattern of genes involved in cortical arealization at P10, before the sensory experience starts (Dye *et al.*, 2012). Moreover, experiments in rats in which enucleations were performed at birth, provoked an increase of the barrel size before active sensory whisking (Fetter-Pruneda *et al.*, 2013; Abbott *et al.*, 2015). Additionally, a recent publication in mice has shown that embryonic enucleation leads to an increase of the barrel size at P4, along with changes in thalamic gene expression (Moreno-Juan *et al.*, 2017). These studies raise the possibility that the barrel cortex expansion is likely due to shifts in the developmental timing of sensory systems, and not due to increased levels of experience-dependent neuronal activity.

It is clear that early plasticity requires cross-talk among deprived/turned off and spared modalities. A putative scenario for inter-modality communication is the thalamus; the brain structure where peripheral sensory inputs from visual, auditory and somatosensory systems converge before reaching the cortex. Indeed, barrel field expansion in embryonically visually deprived mice has been explained using an experience independent model, whereby spontaneous calcium waves in the thalamus during embryonic stages were shown to be a crucial regulator of cortical reorganization (Moreno-Juan *et al.*, 2017). These waves communicate visual, auditory and somatosensory thalamic nuclei before the arrival of the input from the sensory periphery. Both embryonic binocular enucleation and auditory thalamus silencing cause an increase in the frequency of calcium waves in the somatosensory thalamus that predates an enlargement of the cortical barrel-field (Figure 2). At the molecular level, calcium waves were shown to regulate the nuclear orphan receptor Rorβ in the VPM, which increases the complexity of TCA terminals. Thus, this study

demonstrates, on one hand, the existence of a novel mode of communication between distinct sensory-modalities, and on the other hand the mechanism that controls gene expression and triggers barrel size adaptation before the onset of sensory information processing. In sum, intrinsic mechanisms before sensory experience may coexist together with experience-driven activity to promote neuroplastic cross-modal changes after sensory deprivation. The thalamus emerges as a key brain structure to play a role in this early cortical plasticity and therefore, as a potential target for therapeutic interventions.

Concluding remarks

The emergence of the somatosensory cortical map involves the interaction between genes and external input by the environment. What characteristics of the input (trophic or activity-dependent or both) influence the formation of the barrel-field have been recently boosted, especially through the use cell-type-specific manipulation of gene expression and neural activity. Moreover, the role of subcortical regions, such as the thalamus, in controlling the emergence of specific features of the map is gaining emphasis. Thalamic spontaneous synchronous activity not only modulates the formation of the S1 map but also controls its plasticity through the regulation of thalamic gene expression, and ultimately, influencing TCA axonal branching. However, other questions remain opened such as, which are the mechanisms involved in the dendritic refinement of L4 cortical cells? What is the role of the thalamic waves in barrel cortex development? These and other questions should be tackled and responded in the near future.

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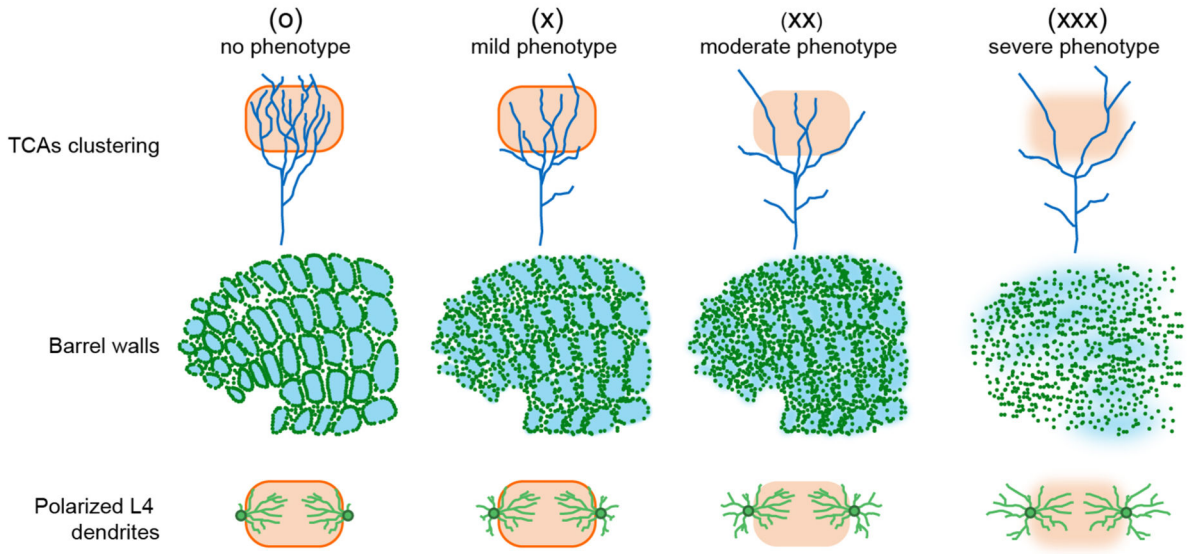
A



B Barrel map defects in mice with tissue-specific genetic manipulations

Protein	Model	Location	TCAs Clustering	Barrel Walls	Polarized Dendrites	Reference
Kir2.1	Tissue-specific Mosaic KO	Cortex - Layer 4	o	o	xx	Egusa et al 2016
AC1	Tissue-specific KO	Cortex	o	o	xxx	Iwasato et al 2008
mGluR5	Tissue-specific Mosaic KO	Cortex - Layer 4	o	xx	xxx	Ballester-Rosado et al 2016
mGluR5	Tissue-specific KO	Cortex	x	xxx	xxx	Ballester-Rosado et al 2010
NMDAR (NR1)	Tissue-specific Mosaic KO	Cortex - Layer 4	o	o	xx	Mizuno et al 2014
NMDAR (NR2B)	Global Mosaic KO	All regions	o	o	xxx	Espinosa et al 2009
NMDAR (NR1)	Tissue-specific KO	Cortex	xx	xxx	xxx	Lee et al 2005 Datwani et al 2002 Iwasato et al 2000
RIM1-RIM2	Tissue-specific KO	Thalamus	x	xxx	xxx	Narboux-Nême et al 2012
AC1	Tissue-specific KO	Thalamus	xx	xx	xxx	Suzuki et al 2015
VGluT1-VGluT2	Tissue-specific KO	Thalamus	xxx	xxx	xxx	Li et al 2013

Figure 1. Increasing severity in barrel map deficits from thalamic to cortical manipulations.

(A) Schematic representation of severity levels in defective phenotypes for three different components of barrel map formation: TCAs clustering (top), alignment to barrel walls of cell bodies from L4 spiny stellate cells (middle), and polarization of their dendritic arbors (bottom). Severity is divided in four categories: no phenotype (circle), mild (one cross), moderate (two crosses), and severe (three crosses). **(B)** Summary of thalamic and cortical tissue-specific manipulation and their consequences in barrel map formation using the severity code described in A.

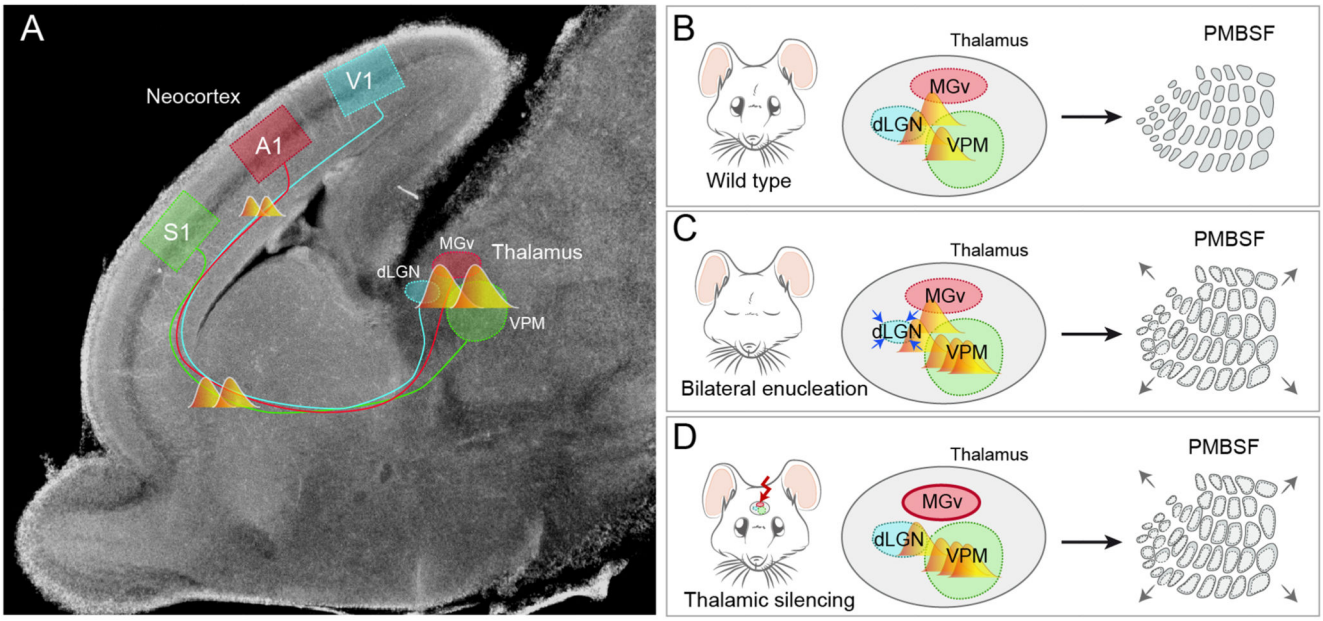


Figure 2. Thalamic calcium waves communicate sensory modalities and regulate S1 barrels formation.

(A) Embryonic Ca^{2+} waves propagate among principal thalamic sensory nuclei and reach the neocortex through thalamocortical axons at E16.5 in mice. **(B)** Bilateral embryonic enucleation at E14.5 triggers more Ca^{2+} waves in VPM and LGN, eventually leading to an increment in barrel size and posteromedial barrel subfield (PMBSF) area. **(C)** Silencing Ca^{2+} waves in the MGv increases Ca^{2+} waves frequency in the VPM. This change precedes barrel and PMBSF area enlargement.

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