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Abstract

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Constraints on somatosensory map development: mutants lead the way.

Short title: mouse mutants show rules of barrel development

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Abstract :

In the rodent somatosensory system, the disproportionally large whisker representation and their specialization into barrel-shaped units in the different sensory relays has offered experimentalists with an ideal tool to identify mechanisms involved in brain map formation. These combine 3 intertwined constraints: 1) fasciculation of the incoming axons ; 2) early neural activity, 3) molecular patterning. Sophisticated genetic manipulations in mice have now allowed dissecting these mechanisms with greater accuracy. Here we discuss some recent papers that provided novel insight into how these different mapping rules and constraints interact to shape the barrel map.

Introduction

Variations in the proportion of brain areas devoted to different sensory modalities (sounds, vision, smell or touch) are striking illustrations of how the brain varies amongst individuals and throughout evolution [1]. More specifically, comparisons of the layout of somatosensory systems in different mammalian species showed that the density of peripheral sensory receptors and their distribution have a impact on the organization and dimensions of the corresponding cortical somatosensory maps [2]. The proportionality between sensory receptors and their brain maps was most strikingly illustrated by the picturesque « homunculus » in humans [3]. In addition to size adjustments, the layout of brain maps also evolves in concert with the nature of the information carried by the receptors under the skin and their organization into specialized sensory organs, which lead to the formation of discrete sensory modules that superimpose upon the topographic maps. The best-known examples are the peculiar distributions of neurons processing sensory inputs from the whiskers in rodents [4] (Figure 1a), or from the nose appendages of the star-nose mole [5].

Because of their recognizable topographic organization but also their adaptation to the layout of the peripheral receptors, somatosensory maps have long served as models in developmental neuroscience to decipher the rules of circuit construction in the brain. These rules combine 3 intertwined constraints (Figure 1b):

- The organization and fasciculation of axons coming from the periphery. Axon fasciculation rationalizes how evolution can accommodate *de novo* changes imposed by the periphery to shape the map without the need of adding novel developmental mechanisms.
- The activity of neurons in different sensory relays. Neural activity acts to strengthen near-neighbor connectivity in the map. Coordinated activity between different sensory relays can explain, in part, how circuits accommodate a growing or shrinking number of receptors in evolution and in pathological contexts such as lesions.
- The molecular patterning of the projection territories in the different relay stations of the brain. Guidance mechanisms act to direct axons and cells, allocating the rough size and the position of the maps. Molecular patterning was thought to be invariable amongst individuals and therefore less prone to adaptation, but it has now been shown to be modulated by sensory inputs.

Establishing how these three constraints are integrated and their hierarchical importance at different stages of development remains a challenge. Mouse genetics, with its ever-increasing specificity to target well-defined neuronal populations has been particularly instrumental in these investigations. Here, we discuss some recent papers that provided novel insight into these different mapping rules/constraints.

The influence of topographic organization of the afferent axons

Recent studies show that a pre-ordering of afferent axons is required to maintain the organization of the map between the different sensory relays. For instance, when thalamo-cortical axons (TCAs) are deviated or scrambled on their way to the cortex the somatosensory map does not form correctly (rev. in [6]). Lokmane et al. analyzed a conditional Ebf1 knock-out, in which TCAs are scrambled because of a defective position of guidepost cells. Surprisingly, they found that although initially mistargeted, TCAs are capable of rewiring postnatally to reach their expected position in the somatosensory cortex. There, they form a rough somatotopic map but then fail to cluster into anatomical and functional barrels corresponding to individual whiskers [7]. This indicates that preserving the relative position of TCAs within the tract is necessary to shape correct map clusters in the cortex; it also highlights the importance of molecular gradients in the cortex to constrain the position and size of the afferent sensory map.

Ordering of trigeminal axons also plays a crucial role in the periphery, between the whisker follicles and the trigeminal nucleus (prV), but a recent study shows that the correct ordering is not sufficient to create a barrel-like organization of the map. Spatial segregation of the main divisions of the trigeminal nerve contributes to the ordering of projections to corresponding dermatomes (mandibular, maxillary and ophthalmic) [8]. More recently, it was shown that row and whisker-specific somatotopic map is already built into the somatosensory brainstem nuclei from the outset [9]. Regarding the requirement of peripheral sensory receptors in driving these modules it has been known for long that the presence of additional whisker follicles on the face leads to the addition of supernumerary barrelettes in the brainstem and of barrels in the cortex [10,11]. However, because the extra follicles were located within the dermatome of the whisker pad (maxillary branch of the trigeminal), it was unclear whether the presence of whisker follicles in any other skin region would be sufficient to instruct barrel formation. Laumonerie and colleagues [9] analyzed Edn1 knock-outs where extra follicles are formed on the lower jaw. Interestingly, innervation to this ectopic whisker pad (from the mandibular branch of the trigeminal nerve) showed no ordered topography, which is the first step of barrelette formation (the latter could not be examined in these mutants because of early lethality). These observations proved that the presence of peripheral receptors is not enough to create *de-novo* barrel clustering in the brainstem, therefore hinting to the presence of unknown cues or factors that are necessary in concert with the peripheral receptors to form barrel-like structures in the brainstem. Molecular cues that are necessary for this organization remain to be identified. These could be located on the axons themselves, and in target territories (which for trigeminal neurons could be either in the skin or in the brainstem) [12] & See discussion below).

Changing the organization of axon trajectories between sensory relays can have a profound influence on the somatosensory map layout. In a conditional knock-out of Robo3 in the brainstem [13], we found a very unusual change in somatosensory map organization (Figure 2a). In those mutants, about two third of the projections between the brainstem trigeminal nucleus (PrV) and the somatosensory thalamus (VPM) are abnormally uncrossed [14]. In the PrV, the cell bodies of crossed/uncrossed neurons are intermixed, although upon exit from the PrV, their routing differs (Figure 2a). Surprisingly, the crossed and uncrossed projections formed two clearly separate cluster in the thalamus, creating two

maps that lay side-by-side with similar orientations relative to the periphery [14,15]. The maps receiving ipsilateral or contralateral inputs were contiguous and organized as mono-blocks. Therefore, the mechanisms controlling the targeting of the projections from the brainstem to the thalamus imposed a segregation between inputs originating from the left or right sides of the face, rather than preserving their correct anatomical positions as defined by genetic pre-patterning. In other words, maintaining the continuity of incoming axonal inputs in the somatosensory target region of the thalamus prevailed over topographic cues. This is a striking difference with the anatomy of the visual thalamus where there is a natural mixing of the left and right retinogeniculate maps. In mutant animals with an excessive number of axons crossing the midline, such as in Siamese cats, the axons that are abnormally crossed project to their correct topographic location and layer in the lateral geniculate nucleus (LGN) (albeit on the wrong side), interrupting the normal map (Figure 2b). Therefore, in the retinogeniculate system, mapping rules that follow the pre-patterned position of the misrouted axons seem to prevail over maintaining the continuity of the retinal inputs [16,17]. This suggests that although a similar developmental genetic framework is shared across modalities [18], the mapping rules may differ in some subtle way between the somatosensory and visual modalities as to which constraints prevail in the organization of the target territories.

The role and origin of spontaneous activity

The role of neural activity in building barrel maps has been established by a series of mouse mutants targeting different components of neural transmission such as presynaptic vesicle release, glutamate and serotonin receptors, or cAMP dependent mechanisms (rev in [19,20]). In all the mutants disrupting normal activity, the general topography of the sensory maps was preserved while axon and/or neuron segregation in layer 4 were perturbed to various extents. A better understanding of these effects was obtained more recently with conditional or mosaic deletions in the thalamus or cortex. For instance, complete suppression of glutamate release at the TCA synapse altered both TCA afferent and layer 4 cortical patterning [21] while depletion of the activity-dependent synaptic release at TCAs affected only the dendritic organization of layer 4 neurons into barrels [22]. Selective ablation of NMDA in the thalamus and mosaic depletion of mGluR5 in the cortex demonstrated the cell autonomous role of these glutamate receptors [23]. Since activity shapes barrel development by postnatal day 5–7, before mice engage in active whisking behaviors, an important question was to identify the source of neural activity, which shows a wide spectrum of different electrophysiological properties across embryonic and early postnatal development (rev. in [24]).

Self-generated activity can be recorded in the cortex of neonatal rat pups [25] and was suspected to arise from spontaneous muscle twitches of the whiskers. Recently, the origin of this activity was studied in greater detail. In one study in rat pups, sensory inputs from the trigeminal nerve was found to be necessary to drive immature activity in the barrel cortex: contact with littermates and the mother were as important as muscle twitches to promote this cortical activity [26]. In another elegant study combining calcium and TCAs imaging in transgenic mice, Mizuno et al. showed that the spontaneous activity of cortical neurons had a remarkable geometric patterning [27]. Synchronous activity was found to be

restricted to the layer 4 neurons that belong to the same prospective barrel as identified by concurrent labeling of TCA afferents. In this study, cortical neuronal activity was driven by the periphery but was uncorrelated to muscle twitches, suggesting some spontaneous activity generated in the periphery. In both studies, the developmental role of synchronized activity was stressed by the fact that it only lasted for the first post-natal week, at the time of barrel formation, after which cortical neuronal activity in the somatosensory cortex became mostly de-correlated.

While neural activity in the post-natal cortex is important to shape the circuits by sharpening the boundaries between barrels, spontaneous activity predates the formation of the cortical maps. The importance of spontaneous activity has recently been also demonstrated in the thalamic relays [28]. Thalamic waves travel through visual, auditory and somatosensory relays and therefore act at the perfect time and place to coordinate the harmonious development of the size of sensory maps and of their relative proportions. The Lopez-Bendito laboratory showed this by genetic manipulation of wave initiation or propagation; in addition, they noted that disrupting the normal propagation of the waves affected the expression of genes controlling thalamic neuron development. Strikingly, thalamic waves occur before the onset of sensory signals. Therefore, evolutionary constraints shaping the prevalence and representation of sensory modalities could potentially act without cues from the periphery. It will be interesting in the future to know whether there are evolutionary mechanisms involving these mechanisms to change the size of the maps. Evolution could indeed produce mutations targeting channels involved in wave generation or their downstream effectors.

Transcriptional cues; interaction with activity.

Mouse genetics and the advent of genomic tools have moved research on barrel development into a molecular and transcriptional era. While earlier genetic studies focused on activity-mutants, as discussed above, some more recent studies unveiled the role of transcription factors, many of which appear to be modulated either by sensory inputs or by neural activity. The modulation by neuronal activity of the expression of transcription factors in several mutants explains how the discrete organization of the somatosensory maps is built from the peripheral modules at all sensory relays.

Periphery-derived molecular signals in the whisker pad regulate both gene expression and branching patterns of the trigeminal ganglionic sensory neurons. For instance, TGF β ligands produced in the whisker follicles signal via smad4 the growth of trigeminal sensory axons and their topographic organization as barrellettes in the first central relay, the PrV [29]. These molecular signals could interact with activity carried by the nerve. Indeed, it was recently shown that a lesion of the trigeminal nerve induces a hyper excitability of prV neurons through a transcriptional mechanism downstream of NMDA receptors [30]. In the following sensory relay, the thalamus, two retinoic-acid related receptors ROR α and ROR β have recently been demonstrated to play complementary key roles for barrel map development. ROR α , the gene mutated in staggerer mutants, is cell autonomously required in the VPM for the growth and modular organization of the TCAs into patterns matching the layout imposed by the periphery [31]. ROR β , although not required for TCA and barrel patterning, was identified as a major

growth promoting factor for the TCAs regulated by spontaneous thalamic activity [28].

In the barrel cortex, as in the thalamus, $ROR\alpha$ and $ROR\beta$ are involved in sensory map formation. $ROR\beta$ expression is regulated by sensory thalamic inputs [32] and its overexpression in the developing cortex is sufficient to impose a clustering of layer 4 neurons, that has some resemblance to a barrel, outside of the normal barrel field [12]. Conversely, $ROR\alpha$ is cell autonomously required in cortical neurons for barrel formation and dendritic remodeling of layer 4 neurons [31]. Few downstream targets of either $ROR\alpha$ and $ROR\beta$ have been characterized as yet. Of note, $ROR\alpha$ controls the expression of the guidance molecules Sema7a, which is known to be required for shaping the dendritic architecture of layer 4 neurons and barrel formation [31,33]. Other transcription factors are positioned upstream of both $ROR\alpha$ and $ROR\beta$ to make layer 4 neurons permissive to TCA ingrowth and promote their assembly as discrete barrels. This is the case of Ctip-1 and Lhx2 [34, 35]. In cortex-specific Ctip1-KO mice all sensory maps and TCAs appear to be disorganized [35] ; labeling of layer 4 neurons with mosaic down regulation of Ctip1 showed that Ctip1-KO neurons were non-permissive to TCAs ingrowth but permissive to cortical callosal projections, seeming to confer to layer 4 neurons a septal-like identity. The cortex-specific deletion of Lhx2 has more subtle effects: TCAs were able to reach layer 4 but did not branch correctly in this layer. This phenotype is reminiscent of the ephrin A5 Efna5-KO [36] and interestingly Efna5 expression is controlled by Lhx2 [34, 37]. Two other genes downstream of Lhx2, AC1 and Btbd3 [37], have also been involved in the activity dependent remodeling of layer 4 neurons around TCAs clusters, again by contributing to constrain the dendritic morphology of these neurons inside a single barrel [38,39]. Overall, while several genes have been shown to affect the polarity of layer IV neuron dendrites, the mechanisms controlling dendrite ingrowth or stabilization inside a single barrel are still unknown.

Conclusion

Overall recent research combining the power of mouse genetics and transcriptomics has substantially increased our understanding of barrel development. These recent studies provided new evidence for a role of axon fasciculation, spontaneous activity, axon guidance and molecular patterning, and further demonstrated their interactions. Among the significant advances are the identification of the different sources of neural activity during barrel development, the demonstration that activity modulates gene expression at different levels of the sensory pathway, and the discovery of new molecular players that are shaping incoming axons into structured maps involving both somatotopic and modular organizations. Fortunately for barrel aficionados, some mysteries remain: one is the role of axon-axon interactions in the wiring of the map, a recurrent theme but which has been difficult to address until now, and that new mutants are bringing to light. The other is the mysterious combination of whisker-derived molecules that sets the whole modular organization of the barrels to a start. Possibly the cellular heterogeneity that exists at all levels in these sensory relay stations will provide interesting novel cues in this regard. Current research along this way, in particular investigating the contribution of non-principal neurons, and of non-neuronal cells to sensory map organization, will be the next episode of this fascinating series.

Figure Legends

Figure 1

1a) The rodent somatosensory brain maps contains a disproportionately large whisker representation. Embedded into the somatotopic map, is a discrete organization of neurons that constitute specialized sensory units. One sensory unit in the periphery (a whisker) corresponds to one well defined neuronal unit in the brainstem (barrelettes in the trigeminal nucleus), in the thalamus (barreloids in the VB), and in the cortex (barrels, in layer 4) b) the three mapping rules and constraints of sensory map formation are diagrammatically illustrated.

Figure 2

Role of axonal organization/ patterning of targets is revealed in mutants where axon routing is modified, such as altered crossing of the midline. A) In robo3-Krox mutants, approx., half the trigemino-thalamic axons abnormally cross the midline. This results in map duplication with parallel topography. B) In the cat visual cortex of Siamese cats, a mutation of the tyrosinase gene increases the number of retinal axons that cross the midline. These misrouted axons, insert into the existing retinotopic map with a correct position.

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A **B**

Axon bundle organization

Early activity

Patterning/Guidance

A **Wild-type Mice** **Robo3-cKO Mice** **B** **Siamese Cats**