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Constraints on somatosensory map development: mutants lead the way

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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 three intertwined constraints: Firstly, fasciculation of the incoming axons; secondly, early neural activity; finally, 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 insights into how these different mapping rules and constraints interact to shape the barrel map.

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Introduction

Variations in the proportion of brain areas devoted to different sensory modalities (sound, 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 major impacts 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 of this organization 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 three intertwined constraints (Figure 1b):

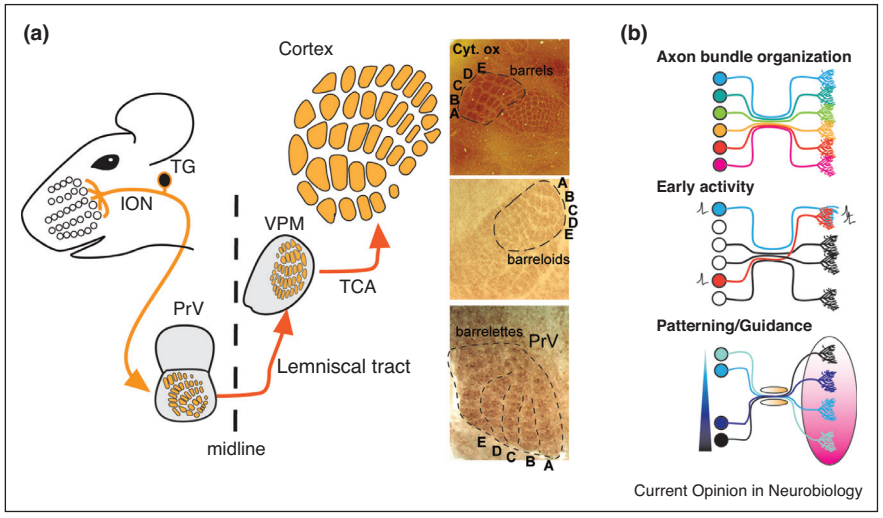
- The organization and fasciculation of axons coming from the periphery. Axon fasciculation rationalizes how evolution can accommodate *de novo* changes imposed by the periphery to shape the map without the need for adding novel developmental mechanisms.
- The activity of neurons in different sensory 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 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

Figure 1



(a) The rodent somatosensory brain maps contains a disproportionally 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.

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