Models of retinotopic development

Stephen J Eglen

University of Cambridge

S.J.Eglen@damtp.cam.ac.uk

SYNONYMS

Topographic map formation, neural map formation, retinogeniculate development, retinocollicular development.

DEFINITION

Axons of neighbouring retinal ganglion cells (RGCs) coming from the eye normally terminate in neighbouring parts of target brain regions, such as the optic tectum of amphibians or the superior colliculus (SC) and lateral geniculate nucleus of mammals. This orderly arrangement of connections is termed a retinotopic map. Theoretical models of retinotopic map formation help us understand how these connections develop in early life, and how maps might reform after surgical or experimental manipulations.

WHAT IS A RETINOTOPIC MAP?

A projection of connections is termed a topographic map when neighbouring neurons in the source region project to neighbouring regions in the target. Topographic maps are found in many sensory systems. Perhaps the most-studied topographic map is the projection from the retina to primary targets in the brain, which ensures that the overall layout of the visual image is preserved as it is sent to the brain (Figure 1). Topographic maps in the visual system are often termed retinotopic maps.

In principle a topographic map can emerge through *local* interactions between neighbouring neurons (Willshaw and Malsburg, 1976). However, local mechanisms alone cannot generate the *global* order observed in maps, whereby one region of the retina consistently projects to the same region of the target in different animals. For example, in mouse, neurons in temporal retina consistently project to anterior SC (Figure 1). Hence, retinotopic maps contain both local and global order.
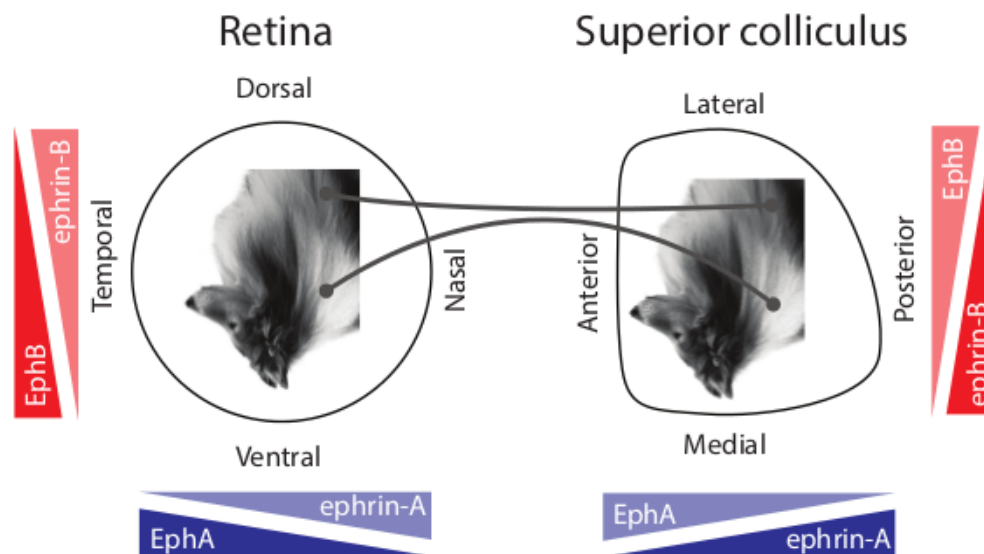

Figure 1: The retinotopic map in the mouse ensures that the retinal image is preserved as it projects to the superior colliculus (SC). Dark red and blue triangles denote the relative expression levels of Ephs and ephrins in retina and SC (see section "1. Molecular gradients"). Lighter triangles indicate counter-gradients. Figure adapted from (Sterratt and Hjorth, 2013) with permission from Cambridge University Press.

MECHANISMS OF MAP FORMATION

Here I describe three key mechanisms proposed to drive the formation of retinotopic maps (Cang and Feldheim, 2013).

1. Molecular gradients

Early experiments into regrowth of retinal axons following surgical manipulations suggested that RGCs tended to regrow to predefined target locations (Sperry, 1963). Sperry therefore proposed that neurons in retina and target had unique molecular labels that encoded this preference (Sperry, 1963). The abilities of such molecular labels to establish retinotopic maps were established computationally by Malsburg and Willshaw (1977), long before any molecular cues had been discovered. The first molecular cues identified were the Eph receptor and ephrin ligand families (Drescher et al., 1997). These proteins are distributed across the retina in a graded fashion (Figure 1) such that neighbouring neurons in retina or target express similar levels of these proteins, and there is a consistent bias (e.g. EphA receptor is always highest in temporal retina).

The mouse visual pathway contains two gradient families, the A system and the B system, across the two axes of retina and target. The A system is repulsive: temporal RGCs have high levels of EphA and terminate in anterior SC, where ephrin-A levels are lowest. Nasal RGCs have low levels of EphA and terminate in posterior SC, where ephrin-A levels are highest. By contrast, the EphB system is attractive, such that ventral retina (with high levels of EphB) projects to medial SC (with high levels of ephrin-B). Cross-talk between A and B systems, counter-gradients (Figure 1) and other proteins may also contribute to map formation (Cang and Feldheim, 2013). Molecular gradients thus provide both local order (neighbouring neurons express similar protein levels) and global order (gradient directions are consistent between animals). A recent computational modelling study has evaluated different hypotheses by which these gradients might contribute to map formation (Triplett et al., 2011).

2. Spontaneous neuronal activity

The pioneering model of Willshaw and Malsburg (1976) proposed that correlated activity in neighbouring RGCs could provide appropriate cues for the development of ordered maps. Experimental evidence for such patterned activity came 14 years later (Maffei and Galli-Resta, 1990). Early in postnatal development, before the retina is visually responsive, RGCs generate spon-

taneous neuronal activity. These activity patterns are often termed 'retinal waves' as the activity propagates across the retina (Wong, 1999). Correlated RGC activity induces correlated activity in mouse target regions (Ackman et al., 2012; Siegel et al., 2012). Hebbian-based activity-dependent refinement can adapt initially weak synapses between RGCs and SC neurons to ensure that (1) SC neurons receive inputs from co-active neighbouring RGCs and (2) neighbouring SC neurons receive inputs from neighbouring RGCs. Activity-based refinement generates local, but not global, order (Willshaw and Malsburg, 1976).

3. Competition for resources

A third key mechanism is that of competition for limited resources. For example, SC neurons can receive only a finite amount of inputs, and RGC axons can make only a limited amount of contacts. Competition comes in many forms, which can be described by a class of mathematical structures (Ooyen, 2001). The importance of competition in map formation can be tested by altering neuronal numbers in either retina or target. Reducing retinal cell numbers affects the maps generated in mouse, but does not alter zebrafish RGC projections (Triplett et al., 2011). Competition can also be used instead of counter-gradients to generate maps (Sterratt, 2013).

Future directions

Many computational models have been proposed for the formation of retinotopic maps (Goodhill and Xu, 2005; Goodhill, 2007), and show how retinotopic order might interact with the development of other map properties, such as ocular dominance or orientation preference (Swindale, 1996). Recent experimental advances in mouse genetics and imaging have generated more quantitative descriptions of retinotopic maps that should help us discriminate which mechanisms are important for map formation. Our recent work (Hjorth et al., unpublished data) suggests that no single model can yet account for all quantitative data on retinotopic map formation in mouse. It is therefore likely that new models are still needed to account for modern experimental results.

Cross-references

- Cortical maps, Activity Dependent Development (348735)

- Cortical maps, Intrinsic Processes (348736)

- Hebbian Learning (348737)

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