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Stimulating issues in cortical map development

What determines the structure of the cortex? Is it encoded in DNA, honed by evolution and ready to spring forth fully formed? Or is it a *tabula rasa*, waiting for the experiences of the developing animal to tune it to the world it encounters? The latter idea has had great appeal beyond the confines of experimental neuroscience. To the mathematically inclined, it offers the promise of understanding the brain by merely uncovering a few simple learning mechanisms. To the politically motivated, it implies a pre-eminent role for nurture over nature, with important implications for public policy. The answer, of course, lies somewhere between the two extremes. But where exactly? Fortunately, experimental research has been gradually yielding hard facts to replace philosophical speculation. The latest installment is an ingenious experiment by Weliky and Katz[1] in the visual system of the developing ferret.

Orientation maps

The primary visual cortex (V1) of mammals contains several maps, that is, regular progressions in the representation of particular features as one moves parallel to the surface of the cortex. The most well-studied of these is the ocular-dominance column map, where the eye preference of cortical cells changes with regular periodicity. A number of properties of this map are known to be activity-dependent[2–5]. The next most well-studied representation is the orientation map. Each neuron in V1 can be characterized as preferring an edge of a particular orientation at a particular position in the visual field, and there is a beautiful map of changing orientation preference moving across the cortex. The degree to which the structure of this map is affected by afferent activity is significantly less clear than for the ocular-dominance map. Does activity determine the direction and magnitude of orientation tuning? Or is the structure of the map somehow prespecified in the cortex, perhaps requiring activity to be realized, but not a function of the precise activity patterns? The orientation tuning of individual cells is known to be sensitive to manipulations of input activity after eye opening (Ref. 6) (for a review see Ref. 7). However, this does not rule out the possibility that default orientation tuning is prespecified. The finding that the visual cortex of cats and monkeys already contains orientation-selective cells at birth seemed to support this idea[8,9]. More recently however, spontaneous activity in the prenatal retina[10], patterned in the form of waves[11], has been discovered. Could this spontaneous activity before eye opening instruct the formation of patterns of orientation selectivity in an unspecified cortex?

Disrupting normal activity

To address this issue, it is necessary to perturb the normal patterns of spontaneous activity experimentally during the emergence of the orientation map. In the cat or monkey, this would require prenatal or very early postnatal intervention, which is extremely difficult. Fortunately, the ferret develops at a similar rate to the cat but is born a month earlier: eye opening does not occur until P31–35 (that is, 31 to 35 days after birth). Recent optical imaging studies have demonstrated the emergence of orientation maps in ferrets between ages P31–36 (Ref. 12). Weliky and Katz[1] inserted a stimulating cuff – a thin cylinder of platinum foil – around one optic nerve at P15–17. The other eye was removed to prevent binocular interactions in the cortex. From then until P41–43, the cuff was activated by 30 Hz biphasic current pulses for 1.8 s every 20 s. The strength of the current was initially small and then increased over time as the animals grew more robust: activation of optic nerve fibres commenced around P27–29. At the end of this period, the orientation and direction selectivity of individual cortical cells was assessed by standard electrophysiological techniques, and the overall structure of the map was observed with optical imaging (Fig. 1). In the stimulated animals, individual cells were much less selective compared to those in the unstimulated controls, similar to those in immature animals. However, the orientation and direction maps seemed unaffected, apart from a decline in overall amplitude commensurate with decreased orientation selectivity. The maps displayed all the usual features, and had a periodicity similar to that in the control animals.

What can be concluded from these results? To start with, they demonstrate directly for the first time that patterns of neuronal activity before and just after eye opening play an important instructive, rather than simply permissive, role in the development of orientation selectivity. However, the issue of the development of the map is less clear. The results are certainly consistent with prespecification. As Weliky and Katz point out though, spontaneous activity is present very early in development, and thalamic axons arrive at the cortex long before artificial stimulation commenced in the experiment. Thus it is possible that an initial map had already been established, too subtle to be detected by optical imaging, but none-the-less guiding the further development of the map along a normal pathway despite the aberrant patterns of activity. Two recent alternating monocular-occlusion experiments in kittens seem to support the idea of a prespecified orientation map. The same map forms again after it has been lost through deprivation[13], and the two eyes form very similar orientation maps even when they have no common visual experience[14]. However, an alternative explanation

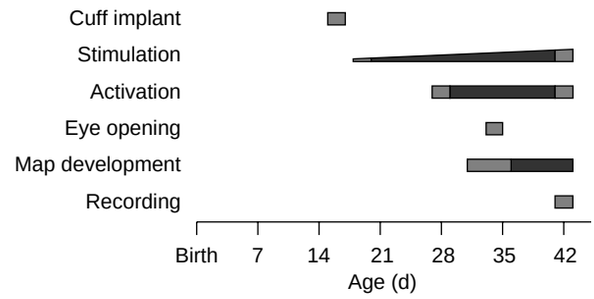

Fig. 1. ***Temporal relationships in the experiment of Weliky and Katz[1].*** *Open boxes represent events whose timing varies between individual ferrets. The stimulus current was gradually increased, so that activation of the optic nerve began some time after current was first applied. Spontaneous activity is present in the retina both before and during the period of stimulation.*

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to prespecification for these results is that the constraints imposed by the shape of the boundary of the target region could interact with a simple self-organizing algorithm to break symmetry in a consistent way[15].

Further questions

One aspect of Weliky and Katz's results that is somewhat mysterious is why artificial stimulation present for such a small proportion of the time (about 10%) had such a large effect on the orientation tuning. It would be interesting to repeat the experiment on a larger scale and examine the dose–response curve as the parameters of the stimulation are changed. A crucial question is, are there effects on the overall map at some proportion greater than 10%? A useful, though very difficult, refinement would be to block the normal spontaneous and visually evoked activity in the retina, perhaps by continuous infusion of tetrodotoxin. Then the effect of the artificially generated activity could be examined uncorrupted by any normal activity. Another mysterious aspect is why the orientation tuning in the stimulated case resembles that found in immature animals. This suggests that perhaps the aberrant activity is simply retarding normal development, rather than sending it off on an altered course as one might have expected.

These results provide important new constraints for evaluating theoretical models for the development of orientation tuning and orientation maps. It would be straightforward to include a small proportion of aberrantly correlated activity into the models: this could be in the form of explicit patterns (for examples see Refs 16,17), or a modification of averaged correlations (for an example see Ref. 18). My initial guess is that a proportion of 10% would have less effect on orientation tuning in the models than in reality.

Ocular-dominance maps

It is interesting to compare the new data with what is known about ocular dominance column segregation. In an experiment that in some ways presaged that of Weliky and Katz, Stryker and Strickland[19] artificially stimulated the two optic nerves of kittens. If left and right nerves were stimulated synchronously, ocular dominance column segregation did not occur in the cortex, whereas asynchronous stimulation led to a crisp pattern. It would be fascinating to include such a binocular component into the paradigm of Weliky and Katz. Löwel[5] recently demonstrated a change in overall ocular-dominance column periodicity with strabismus in the cat: columns became wider, a result that was predicted theoretically[20]. More recent theoretical work predicts a change in the overall direction of flow of ocular-dominance columns given particular activity patterns[21]. However, few predictions exist yet for how manipulating afferent activity might change the overall structure of orientation maps. Since, in some species, the structure of orientation maps is quite closely tied to that of ocular-dominance maps[22], changes to the latter might imply changes to the former. An intriguing recent result is that in strabismic squirrel monkeys, the normal relationship between ocular-dominance columns and cytochrome-oxidase blobs is not present[23]. However, the relationship between cytochrome oxidase blobs and orientation maps is still controversial[24,25].

Concluding remarks

Weliky and Katz have made an important contribution to our knowledge of how the primary visual cortex develops. The results prompt several further questions that could be addressed using their experimental paradigm about the relative contributions of activity-dependent versus activity-independent processes. More generally, the new data feed into the long-standing debate about prespecification in the cortex as a whole[26,27]. Whether you are an experimentalist, a theoretician or a politician, progress in untangling the factors that determine cortical structure is a topic that will continue to deserve your attention.

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