Part II:
Cortical Maps and Receptive Fields

Nature vs. Nurture in the Development of Tangential Connections and Functional Maps in the Visual Cortex

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Abstract. A series of experiments concerned with mechanisms underlying the development of the visual cortex revealed that long-range tangential connections display at least the following three characteristics: i) in strabismic but not in normally raised cats, intracortical fibers preferentially connect cell groups activated by the same eye ('ocular dominance selectivity'), ii) within the subsystems of the left and right eye domains, they extend primarily between neurons activated by similar stimulus orientations ('orientation selectivity') and iii) they exhibit an anisotropy with respect to the cortical axes by preferentially linking neurons with colinearly aligned receptive fields ('axial specificity'). These results are compatible with the idea of a selective stabilization of tangential fibers between coactive neurons (the "fire together, wire together"-hypothesis). Optical imaging of functional maps in area 17 of strabismic cats further revealed that iso-orientation domains are continuous across the borders between adjacent ocular dominance columns. This rather supports an experience-independent initial development of orientation preference maps. To what extent spontaneous versus visually driven activity patterns might be involved both in the development of tangential connections and in functional maps is discussed.

1 Intrinsic connections

The specific capabilities of our brains depend critically on the interactions of a large number of neurons. For a thorough understanding of the working of brains it is therefore indispensable to know the connectivity patterns and the functional interactions between these groups of neurons. A characteristic feature of the visual cortex of ferrets, cats and monkeys is the existence of long-ranging tangentially oriented axon collaterals that interconnect regularly spaced clusters of cells. In kitten visual cortex, tangential connectivity patterns develop mainly after birth from an initially rather homogeneous distribution of interconnected neurons. Evidence accumulated in the last years indicates that the adult specificity is attained in an experience-dependent way. A very fruitful working hypothesis to elucidate the mechanisms underlying the development of these connections turned out to be the "wire together, fire together"-hypothesis.

According to this hypothesis (based on ideas developed by [1]), connections between two neurons are stabilized when the cells are active in synchrony, while connections are weakened and finally get lost in out-of-synchrony constellations. We were able to gather evidence in favor of this hypothesis in a series of experiments in the visual cortex of strabismic cats. In these animals, the optical axes of the two eyes are no longer aligned so that the images on the two retinae cannot be brought into register. As a consequence, the responses mediated by anatomically corresponding retinal loci in the two eyes are no longer correlated.

If there is selective stabilization of connections between those cells that exhibit correlated activity while the animals grow up, intracortical connections in strabismic animals should display at least the following three characteristics: i) they should extend primarily between neurons driven by the same eye (experiment I), ii) within the subsystems of the left and right eye domains, they should extend primarily between neurons preferring similar stimulus orientations (experiment II). Since in our visual world contrast borders are mostly elongated (at least over short distances), neurons with colinearly aligned receptive fields should have a very high probability of being coactivated. Therefore, iii) intracortical connections should extend primarily between neurons whose receptive fields are aligned colinearly (experiment III). These predictions were tested by an approach combining the following methods: we first visualized the functional architecture of primary visual cortex (area 17) of cats with optical imaging of intrinsic signals [2] and then injected retrograde tracers into functionally identified cortical domains. Finally the resulting connectivity patterns were superimposed on and quantitatively compared with 2-deoxyglucose (2-DG) labeled activity maps of the same cortical regions [3-5].

Experiment I: In area 17 of strabismic but not normally raised cats, tangential intracortical fibers preferentially connected cell groups activated by the same eye [3]. Experiment II: 50-70% of the retrogradely labeled neurons were located in the same eye/same orientation (OR-) domains visualized with 2-DG while these occupied only about 30% of the cortical surface (see also [6,7]). Experiment III: After injections of beads into horizontal OR-columns, the distribution of retrogradely labeled cells was elongated along the cortical representation of the horizontal meridian (Figure 1). Injections into vertical OR-columns revealed anisotropies of the cell plots along the vertical meridian [4]. In both cases, neurons with receptive fields that are aligned colinearly in visual space had more numerous tangential connections (see also [8]).

Taken together, these anatomical results are all compatible with the idea of a selective stabilization of tangential fibers (during early postnatal development) between coactive groups of neurons. They thus support the hypothesis that the strength of intrinsic connections in the primary visual cortex of adult cats reflects the frequency of previous correlated activation. The experimental evidence appears convincing for the 'ocular dominance selectivity' of the tangential fibers, since these fibers connected cell groups activated by the same eye only in strabismic but not in normally raised cats [3]. The situation is less clear for the 'orientation selectivity' and 'axial anisotropy' of the tangential fibers. There
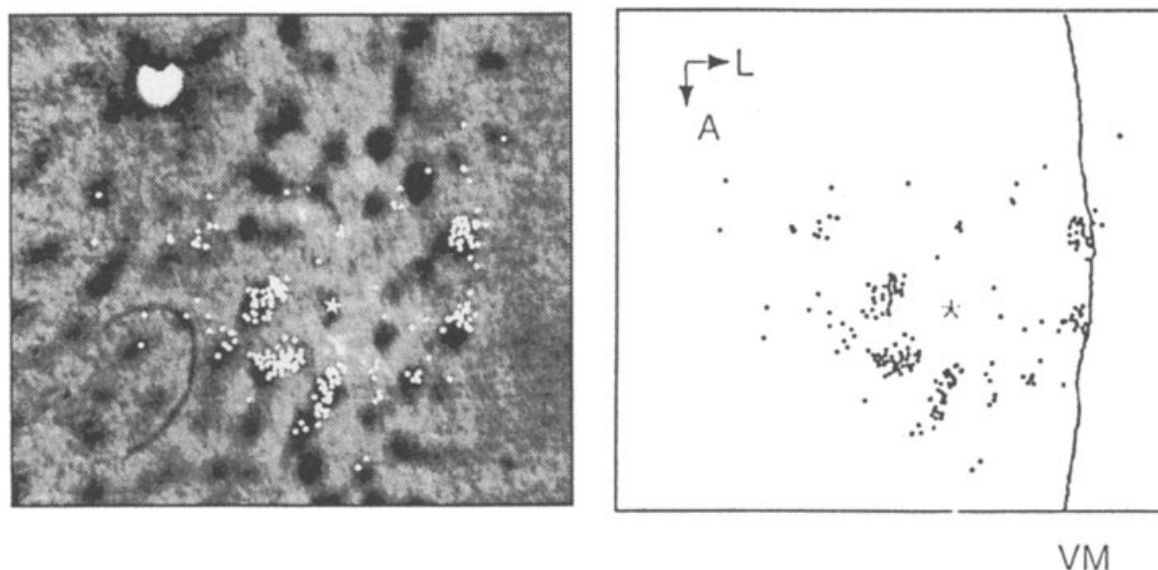
Fig. 1. Functional specificity of tangential connections in the primary visual cortex (area 17) of cats. (A) Autoradiograph of a flat-mount section demonstrating the layout of 2-DG labeled monocular OR-columns of a strabismic cat whose right eye had been stimulated with moving horizontal gratings. After an injection of green beads into a column preferring these gratings (marked with a white asterisk), retrogradely labeled neurons (white dots) are in register with the 2-DG labeled OR-domains. (B) Schematic drawing of the labeled neurons (black dots) relative to the cortical axes (VM=vertical meridian, continuous line). The distribution of labeled cells is elongated along the horizontal meridian (orthogonal to the VM). Note that tangential connections display both modular (A) and axial (B) specificity. L, lateral, A, anterior.

is no systematic investigation to date on parameters or rearing conditions that abolish or change one or the other component as was the case for the strabismic cats. Recently, modular and axial selectivity of tangential fibers was even reported in the visual cortex of very young tree shrews as early as 1-3 weeks after eye opening [9]. It thus seems that either a small amount of visual experience is already sufficient or that visual experience is not needed at all for establishing the modular and axial specificity of horizontal connections as seen in adult animals. On the other hand, the recent evidence that blockade of cortical but not of retinal activity prevents the initial development of clustered horizontal connections in area 17 of ferrets clearly demonstrated that neuronal activity is necessary for the development of tangential connections [10]. The role of spontaneous activity waves in this process is a highly debated issue at the moment but its exact role for both the development of intrinsic connections and cortical maps remains to be determined. The close relationship between intrinsic connections and OR-columns indicates that experience-independent mechanisms might also play a role in the development of the latter system.

2 Functional maps

Accumulating evidence suggests that maps of OR-preference might develop according to different rules compared to the system of OD-columns: while it is clearly established that the segregation of thalamo-cortical afferents into alternating OD-columns is driven by activity-dependent competition between the two sets of afferents for cortical territory, and that correlated activity seems to be the major organizing principle for the development of OD-columns (for review see [11]), visually driven activity seems to play a less important role for OR-preference maps to develop. In both area 17 of ferrets and area 18 of cats, OR-preference maps are present already one week after eye opening and their layout does not seem to change dramatically in the following two weeks [12,13]. In addition, OR-maps are identical for the two eyes in cats raised without binocular visual experience [14,15]. While the latter two studies were concerned with the development of cortical maps in area 18, we focused our attention on area 17 in strabismic cats. If visually driven correlated activity played an equally important role for the development of OR-columns as it does for the development of OD-columns, then OR-domains activated by different eyes should distribute independently, i.e. they should not be continuous across the boundaries between different OD-domains. A continuous course of OR-domains across OD-borders, however, would support an experience-independent initial development of OR-columns as suggested for area 18.

To distinguish between these two possibilities, we visualized the layout of iso-OR- and OD-columns in area 17 of strabismic cats using optical imaging of intrinsic signals, and analyzed the topographic relationship between the two functional systems [16,17]. Optical imaging revealed segregated OD-columns since monocular iso-OR-domains were different for the left and right eye. Most interestingly, iso-OR-columns were continuous across OD-borders (Figure 2A). Quantitative analysis indicated a preponderance of steep intersection angles between iso-OR-contours and OD-columns (Figure 2B) [16,17].

Imaging of the functional architecture of area 17 in strabismic cats revealed that iso-OR-columns are continuous across the borders between different OD-columns. In light of classical experiments about the development of OR-selectivity in single neurons (for a review see [18]) and the more recent imaging experiments in cat area 18 [14,15], the most likely explanation for this observation is that the basic layout of OR-preference maps is specified before the age at which OD-columns start to segregate (about three weeks postnatally) and thus before experience (and hence visually driven activity) begins to influence the development of cortical architecture (the "critical" period; e.g. [19]). This does not imply that neuronal activity plays no role in organizing OR-maps. As briefly discussed above for intrinsic connectivity patterns spontaneous activity waves are also ascribed a role in the expression of functional maps in the visual cortex. Traveling waves of both cortical [20] and thalamic [21,22] origin have been observed so far and thus could instruct the initial layout of OR-maps and the early clustering of tangential connections.
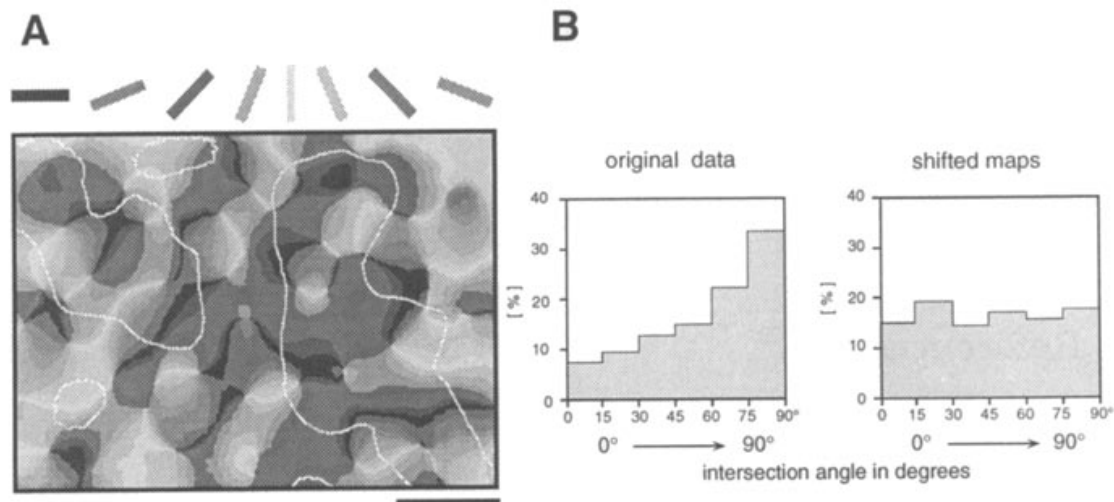
Fig. 2. Topographic relationship between iso-OR- and OD-columns in the visual cortex of a strabismic cat. (A) Superposition of the OR-preference ('angle') map and the outlined borders of adjacent OD-columns (white contours). The preferred OR for every region in the imaged cortex is coded by gray levels according to the scheme on the top of the figure. Scale bar 1mm. (B) Histograms of intersection angles between iso-OR- and OD-columns. x-axis, intersection angle in degrees from $0°$ to $90°$ (divided into 6 classes); y-axis, percentage of intersection angles in the respective class. Left histogram, original data; right histogram, shifted maps: iso-OR-contours of one animal superimposed with the OD-borders of another animal. Note that domains of like OR-preference labeled by the same gray in the angle map are continuous across the borders of adjacent OD-domains and that intersection angles between $75°$ and $90°$ are most abundant in the original data.

According to the proposed scenario, the development of OR-maps precedes that of OD-columns (at least in cats). Therefore the spatial arrangement of OD-columns should be influenced by the layout of the preexisting OR-map. The fact that iso-OR-contours tend to intersect the OD-borders at steep angles indeed indicates a systematic topological relation between the two maps as originally suggested by [23], and previously observed in macaque monkey striate cortex [24,25]. To what extent there are differences in the layout of OR-columns between strabismic and normally raised cats awaits the detailed analysis of these maps in normal animals.

3 Conclusions

Studies of both the development of tangential connections and functional maps demonstrated that experience and hence visually driven activity play a major role in the structuring of the visual cortex. However, recent experiments also revealed limits of the "experience-dependent" ("nurture") concept and pointed

towards spontaneously generated neuronal firing patterns as an additional organizing principle of cortical development.

4 Acknowledgements

5 References

[1] Hebb, D.O. (1949) The organization of behavior. A neuropsychological theory. New York: Wiley.

[2] Grinvald, A., Lieke, E., Frostig, R.D., Gilbert, C.D. and Wiesel, T.N. (1986) Nature 324: 361-364.

[3] Löwel, S. and Singer, W. (1992) Science 255: 209-212.

[4] Schmidt, K.E., Goebel, R., Löwel, S. and Singer, W. (1997a) Europ. J. Neurosci. 9:1083-1089

[5] Schmidt, K.E., Kim, D.-S., Singer, W., Bonhoeffer, T. and Löwel, S. (1997b) J. Neurosci., 15:5480-5492

[6] Gilbert, C.D. and Wiesel, T.N (1989) J. Neurosci. 9: 2432-2442.

[7] Malach, R., Amir, Y., Harel, M. and Grinvald, A. (1993) Proc. Natl. Acad. Sci. USA 90: 10469-10473.

[8] Bosking, W.H., Zhang, Y., Schofield, B. and Fitzpatrick, D. (1997) J. Neurosci. 17: 2112-2127.

[9] Crowley, J.C., Bosking, W.H., Foster, M. and Fitzpatrick, D. (1996) Soc. Neurosci. Abstr. 22: 404.10.

[10] Ruthazer, E.S. and Stryker, M.P. (1996) J. Neurosci. 16: 7253-7269.

[11] Stryker, M.P. (1991) In: Development of the visual system (Lam, D.M.-K. and Shatz, C.J., eds.), pp 267-287. Cambridge, MA: MIT Press.

[12] Chapman, B., Stryker, M.P, and Bonhoeffer, T. (1996) J. Neurosci. 16: 6443-6453.

[13] Gödecke, I., Kim, D.-S., Bonhoeffer, T. and Singer, W. (1997) Europ. J. Neurosci. 17:in press.

[14] Gödecke, I. and Bonhoeffer, T. (1996) Nature 379: 251-254.

[15] Kim, D.-S. and Bonhoeffer, T. (1994) Nature 370: 370-372.

[16] Löwel, S., Schmidt, K., Kim, D.-S., Singer, W. and Bonhoeffer, T. (1994) Eur. J. Neurosci. Suppl. 7: 48.06.

[17] Schmidt, K.E., Kim, D.-S., Singer, W., Bonhoeffer, T. and Löwel, S. (1994) Soc. Neurosci. Abstr. 20: 137.7.

[18] Henry, G.H., Michalski, A., Wimborne, B.M. and McCart, R.J. (1994) Prog. Neurobiol. 43: 381-437.

[19] Wiesel, T.N. (1982) Nature 299: 583-591.

[20] Huttenlocher, P.R. (1967) Exp. Neurol. 17: 247-262.

[21] Kim, U., Bal, T. and McCormick, D.A. (1995) J. Neurophysiol. 74: 1301-1323.

[22] McCormick, D.A., Trent, F. and Ramoa, A.S. (1995) J. Neurosci. 15: 5739-5752.

[23] Hubel, D.H. and Wiesel, T.N. (1977) Proc. R. Soc. Lond. B 198: 1-59.

[24] Bartfeld, E. and Grinvald, A. (1992) Proc. Natl. Acad. Sci. USA 89: 11905-11909.

[25] Obermayer, K. and Blasdel, G.G. (1993) J. Neurosci. 13: 4114-4129.