Development and Plasticity of the Cerebral Cortex: From Molecules to Maps

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Received 10 May 1999; accepted 20 May 1999

ABSTRACT: The role played by environmental influences in the development of the nervous system has been subject to intense study for the last three decades. Many laboratories are currently engaged in characterizing the exact contributions of activity-dependent or -independent processes to the development of the mammalian neocortex. Here we introduce a special issue devoted to the topic and briefly review recent progress in this exciting field. At the systems level, many investigators are now distinguishing between an "establishment" phase of cortical connections, where activity-dependent and independent mechanisms could operate, and a later "maintenance" phase, which appears to be controlled by neuronal activity. A particularly interesting recent example of the role of top-down vs. bottom-up influences in the development of cortical connections is the emergence of orientation selectivity in visual cortex: we propose a synthetic view highlighting the role of the thalamo-cortical reciprocal projection in this process. Finally, at the cellular level, NMDA receptors, neurotrophins and many other molecules contribute to activity-dependent rearrangement of cortical connections during appropriate critical periods of development. © 1999 John Wiley & Sons, Inc. J Neurobiol 41: 1–6, 1999

Understanding how the cerebral cortex, with its roughly 10^{11} neurons and 10^{15} synapses, develops is one of the most important questions in neuroscience. Some of the rules governing cortical development in mammals must be similar to the rules that regulate development of other brain structures. But the cortex is also special, not only for its sheer size and complexity but also for the enormous sophistication of the tasks it performs. We present in this special issue of the *Journal of Neurobiology* a collection of articles that cover recent experimental and theoretical approaches to understanding cortical development. The question we focus on is: What are the cellular and circuit mechanisms responsible for the activity-dependent organization and rearrangements of cortical development? This problem, first formulated in modern terms over 30 years ago in the now classical work of Wiesel and Hubel, addresses directly the fundamental question of whether the development of the nervous system is a result of innate factors (nature) or environmental influences (nurture). This issue, incidentally, has constituted one of the key debates in Western culture since John Locke first proposed the idea that the mind is an "empty cabinet," or *tabula rasa*, where percepts accumulate, and is therefore shaped by its sensory environment (Locke, 1669).

The field of activity-dependent cortical development has been dominated by studies of the visual cortex. Wiesel and Hubel demonstrated that the development of ocular dominance and binocularity in the primary visual cortex of cats was influenced by sensory activity during a critical period of develop-

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 CCC 0022-3034/99/010001-06

ment (Wiesel and Hubel, 1963, 1965; Hubel and Wiesel, 1965). In later work, together with their students, they extended these results to the monkey and showed both major anatomical and physiological consequences of even short periods of sensory deprivation (reviewed in Wiesel, 1982). During the 1980s, several lines of evidence, including the previous demonstration that the initial development of ocular dominance columns occurred prenatally in monkeys (Rakic, 1977) and that binocularly deprived kittens had relatively normal cortical development (Wiesel and Hubel, 1965), led to a special emphasis on the role of spontaneous activity in the developing nervous system. Indeed, blocking spontaneous retinal activity prevented the normal segregation of ocular dominance columns in cortex (Stryker and Harris, 1986) and retinal afferents in the lateral geniculate nucleus (Shatz and Stryker, 1988). The role of spontaneous activity was further substantiated by the discovery of spontaneous correlated activity in developing retina (Meister et al., 1991) and developing neocortical slices (Yuste et al., 1992). In the recent past, besides this continuing focus on the role of spontaneous activity (Shatz, 1990; Katz and Shatz, 1996), a major direction has been the examination of orientation selectivity and orientation columns as exemplars of pattern formation and connectivity in visual cortex during development.

The search for specific cellular mechanism responsible for cortical plasticity during development started with Wiesel and Hubel's prediction for a competition-based mechanism, which was framed by Stent in a symmetric version of the well-known Hebb algorithm (Stent, 1973). An easily remembered version is the adage, "Neurons that fire together, wire together" (Loewel and Singer, 1992), and the complementary "Neurons that are out of synch, fail to link" (S. Loewel and M. Bear, personal communication). In the past 15 years, an explosion of studies has examined the possible role of candidate molecules for explaining the critical period and its mechanisms. Although there is growing consensus about the important roles that *N*-methyl-D-aspartate (NMDA) receptors and neurotrophins play in this plasticity, the search for molecular mechanisms is ongoing in an increasing number of laboratories. At the same time, many investigators are focusing on a better understanding of the basic phenomenology of cortical development and plasticity and the exact role that activity plays in it.

DEVELOPMENTAL PLASTICITY: ESTABLISHMENT AND MAINTENANCE OF CORTICAL CIRCUITS

The major model systems in this field have been the formation of ocular dominance columns in visual cortex, the development of orientation selectivity and orientation columns in the visual cortex, and the development of the "barrel field" in rodent somatosensory cortex. Work on all three systems is represented in this special issue. As in well-studied forms of hippocampal synaptic plasticity, most investigators in neocortical developmental plasticity now distinguish between an initial phase of establishment and a subsequent phase of maintenance. This distinction is not merely academic: Whereas spontaneous activity and perhaps genetic factors play a role in the establishment of the system, visual experience appears necessary for its maintenance.

In retrospect, it is somewhat surprising that the idea that there may be two phases to cortical plasticity is only now being fully appreciated, for its roots have been present since the earliest findings (Wiesel, 1999). Hubel and Wiesel (1963) and Wiesel (1982) showed that even newborn kittens and monkeys had orientation-selective cells in their visual cortex, while rearing under different conditions was shown to degrade or alter orientation selectivity. Similarly, Rakic (1977) showed that while newborn monkeys had well-formed ocular dominance columns, postnatal monocular lid suture actually altered the columns. In the past few years the distinction between establishment and maintenance of cortical circuits has been reexamined, mostly because of the application of optical imaging to assay the development of orientation maps in visual cortex and the effects of rearing manipulations on these maps.

There is substantial agreement that the initial development of orientation-selective responses and of orientation maps does not require a significant role for visually driven activity (Chapman et al., 1999; Schmidt et al., 1999; Crair et al., 1998). Two alternative scenarios are proposed to account for this initial developmental stage: correlated spontaneous activity in afferents, or molecular specification due to activity-independent intrinsic (genetic) factors. The discovery of highly correlated spontaneous activity in the Lateral Geniculate Nucleus (LGN) (demonstrating intraocular, interocular, and center-type correlations) (Weliky, 1999) provides a possible role for spontaneous thalamic activity in this process that may override or amplify the effect of retinal waves in the system (Miller et al., 1999; Weliky, 1999). Since LGN activ-

ity is influenced by the massive feedback cortico-thalamic projection, spontaneous activity in the cortex actually plays an important role in regulating the spontaneous activity in the thalamus. Indeed, it is possible that orientation selectivity might actually be primarily determined by intracortical interactions, while subsequent activity-dependent selection of the correct thalamic inputs could follow to ensure that the thalamic and cortical circuits are in register (Schmidt et al., 1999). On this top-down viewpoint, the cortex sets up the orientation map and imposes its specificity on thalamocortical synapses. Such a scheme can potentially explain diverse experimental data that all demonstrate little effect on orientation maps despite significant manipulation of afferent activity: Altering the pattern of afferent activity does not change orientation maps, while it degrades orientation tuning (Weliky, 1999); reverse eyelid suture leads to a precise restoration of the orientation map (Kim and Bonhoeffer, 1994), and alternating monocular suture still leads to precisely aligned maps from the two eyes (Goedecke and Bonhoeffer, 1996). The scaffold of horizontal clustered connections that girds the cortical map of orientation may itself be created by activity in the subplate and the marginal zone. Indeed, blockade of activity in the subplate produces misguided thalamic connections (Catalano and Shatz, 1998), and spontaneous correlated activity among spatially separated neurons is found in the marginal zone of intact hemisphere preparations (Schwartz et al., 1998). Incidentally, the idea that thalamo-cortical synapses may follow the intracortical specification of orientation through an activity-dependent selection could also reconcile results showing specificity in the thalamic innervation of simple cells (reviewed in Hubel, 1996), together with the fact that thalamic synapses constitute a very small percentage of the total number of synapses that these same simple cells receive (Ahmed et al., 1994)—data which therefore point instead at the cortical network as the major driving input to these cells.

Nevertheless, the network of horizontal connections cannot specify which orientation is represented at which precise set of cortical loci. Indeed, there are a variety of data that suggest that bottom-up influences are crucial. A model system in which the issue has been addressed is the "rewired" visual projection in ferrets (Angelucci et al., 1998), in which retinal inputs are directed to the auditory thalamus, and visual inputs drive auditory cortex (Sur et al., 1999). Single neurons in the rewired auditory cortex are as well tuned for orientation as are neurons in visual cortex. Thus, the same mechanisms of tuning are likely at work: Thalamic inputs provide orientation biases that are amplified by recurrent local cortical networks to generate sharp orientation specificity (Ben-Yishai et al., 1995; Douglas et al., 1995; Somers et al., 1995). The orientation map in rewired cortex, on the other hand, is less periodically organized than in visual cortex. Thus, the orientation selectivity of individual neurons is separable from their organization into an orientation map. Long-range horizontal connections in rewired cortex are also less periodically clustered than in visual cortex; however, they are more so compared to normal auditory cortex. Thus, similar to the effects of artificial strabismus on horizontal connections in visual cortex (Schmidt et al., 1999), visual inputs to the rewired cortex (that set up orientation specificity and specify the retinotopic map of visual space) do shape long-range connections, but to an extent that is limited by the intrinsic features of the cortex. Thus, a unified synthesis can be proposed, in which reciprocal thalamo-cortical interactions seem necessary for both the generation of orientation selectivity as well as for determining the organization and plasticity of orientation maps. Unfortunately for experimenters, disentangling the separate role of each component of the loop might not be easy. Finally, a critical question remains: How are the local circuits that generate orientation selectivity related to the long-range circuits that map this orientation in the visual cortex?

A scenario which is not mutually exclusive with a role for spontaneous activity is that the initial specification of orientation and orientation maps is genetically determined. This hypothesis is considered by several contributors (Chapman et al., 1999; Miller et al., 1999; Weliky, 1999). Although orientation maps appear to be too complex for molecular specification, reaction-diffusion models based on a small number of molecules can explain complex pattern formation (Turing, 1952). To test genetic specification, the thought experiment of imaging the orientation maps of isogenic animals is proposed (Chapman et al., 1999), although it is debatable what a positive result (identical orientation maps in isogenic animals or identical twins) would actually mean (Miller et al., 1999). In any case, experiments exploring the possible molecular basis for the development of orientation selectivity or orientation maps seem definitely worth doing, since this issue lies at the heart of the nature/nurture debate.

In contrast to the establishment of orientation selectivity, there is widespread agreement that its maintenance is influenced by visual activity. This separation of establishment and maintenance can help interpret apparently contradictory results over the last decades (Wiesel, 1999). Recent experiments involv-

ing lid suture demonstrate that visual experience has a clear effect on the maintenance of orientation maps, with nondeprived inputs competing for cortex devoted to deprived inputs (Crair et al., 1997, 1998). Similarly, in the barrel cortex, the effect of deprivation is related to the proximity to active, nondeprived inputs (Wallace and Fox, 1999). These findings raise the issue of whether cortical maps in general are important functionally. Experiments in the barrel cortex comparing the spatial extend of plasticity suggest that the actual map serves to set up a functional memory trace (Diamond et al., 1999).

MECHANISMS OF DEVELOPMENTAL PLASTICITY: NMDA RECEPTORS AND NEUROTROPHINS

A second major topic that many contributions to this special issue address is the nature of the specific cellular or molecular mechanisms responsible for developmental plasticity in neocortex. Much work has concentrated on testing the role of the NMDA type of glutamate receptors and neurotrophins in this process, while some results are starting to highlight some novel, presumably downstream molecular pathways that could play important roles.

The simplest hypothesis for implementing activity-dependent plasticity is the existence of mechanisms that can detect the correlation of activity between pre- and postsynaptic elements and translate that information into a strengthening of the correlated synapses and elimination of the noncorrelated ones, following a symmetric Hebbian rule (Stent, 1973; Frégnac and Shulz, 1999) or a BCM algorithm (Bear and Rittenhouse, 1999). Interestingly, developmental plasticity in a completely unrelated system, the neuromuscular junction, can also be implemented by formally similar mechanisms (Balice-Gordon and Lichtman, 1984; Jennings, 1994).

The main candidate for a coincidence detector at synapses in the central nervous system is the NMDA receptor, which can translate the temporal coincidence of pre- and postsynaptic activity into very high ($>20\ \mu M$) intracellular $[Ca^{2+}]_i$ transients at activated spines (Yuste et al., 1999) and trigger the formation of new spines in neurons that undergo potentiation (Engerts and Bonhoeffer, 1999). In agreement with the NMDA receptor hypothesis for cortical developmental plasticity, blocking NMDA receptors can prevent the rearrangements in eye-specific connections following monocular lid suture (Kleinschmidt et al., 1987). A concern is that NMDA receptors have a major role in ongoing synaptic transmission in the cortex (Tsumoto et al., 1987; Miller et al., 1989; Fox and Daw, 1990), and blocking them may lead to nonspecific effects related to a reduction in transmission rather than a specific effect on development. Nevertheless, several lines of evidence, including suppressing NMDA receptor function using antisense DNA to block ocular dominance plasticity without affecting visual responses (Roberts et al., 1998), demonstrate that NMDA receptors do play a major role in cortical developmental plasticity. Indeed, long-term potentiation and long-term depression following classical Hebbian paradigms occurs in thalamo-cortical synapses during the critical period (Feldman et al., 1999; Bear and Rittenhouse, 1999). If the earliest synapses are "silent," i.e., only have NMDA receptors and lack AMPA receptors, correlated activity producing LTP could serve to turn on the correct complement of synapses, sculpted out of an initially random connectivity (Feldman et al., 1999). Besides NMDA receptors, subclasses of glutamate metabotropic receptors linked to release of calcium from internal stores (Berridge, 1998) could also play an important role during the critical period and also formally fulfill the coincidence detector condition (Daw et al., 1999).

The most investigated molecules that could mediate the presynaptic rearrangements secondary to the detection of correlated activity (or the elimination of connections due to lack of correlated activity) are the neurotrophins (Berardi and Maffei, 1999; Black, 1999; Shieh and Ghosh, 1999). Neurotrophins are released by postsynaptic neurons in an activity-dependent fashion (Barde, 1994), so they are also ideally suited to implement the retrograde signal from the postsynaptic dendrite to the presynaptic terminal. While NGF administration can interfere with cortical plasticity (Berardi and Maffei, 1999), brain-derived neurotrophic factor (BDNF) can alter the maturation of GABAergic interneurons (Huang et al., 1998). BDNF and neurotrophin-3 (NT3) also have antagonistic effects on dendritic morphology that depend on the particular type of the neuron (McAllister et al., 1997). Finally, trkB, the receptor for BDNF and NT4-5 (Black, 1999), is involved in the formation of ocular dominance columns (Cabelli et al., 1997). These many effects of different neurotrophins paint a complicated picture. To reconcile the experimental data, Berardi and Maffei propose a circuit hypothesis that can serve as a road map of the neurotrophins effects and can be experimentally tested.

Finally, several lines of work are exploring the downstream mechanisms that read the activity patterns and translate them into structural rearrangements. Calcium-calmodulin kinase 4 could sense the high $[Ca^{2+}]_i$ produced by correlated activity and

switch on specific gene expression program (Shieh and Ghosh, 1999). Other genes could play important roles at different stages of the process: Libraries enriched in "plasticity" genes are producing many interesting candidates, and the analysis of their function has only started (Nedivi, 1999; Quinn et al., 1999; Corriveau, 1999).

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