Activity-dependent remodeling of connections in the mammalian visual system

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The development of precise connections in the mammalian central nervous system requires neural activity. Synchronous patterns of afferent activity, and coincident afferent and target activity are required for specifying the neuronal connectivity that characterizes the adult visual pathway in mammals. During development, postsynaptic target neurons communicate with presynaptic afferents. Recent evidence suggests that the mechanisms that underlie activity-dependent development of connections in the visual system may share significant similarities with the mechanisms responsible for synaptic plasticity in the adult brain.

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Introduction

The precise pattern of connections that characterizes many neural pathways arises from a combination of intrinsic, activity-independent determinants and activity-dependent cues. The visual system of mammals has been particularly important in demonstrating the role of neuronal activity in the development of the precise connections that characterize specific pathways in the adult brain, and many of the key ideas that constitute our current framework for understanding activity-dependent development have been formulated from this work. We review here the evidence that afferent activity plays a role in shaping connections in the visual thalamus and cortex, discuss an hypothesis for the mechanisms whereby activity shapes connectivity, and describe recent experimental results that address the hypothesis.

Afferent activity and visual development

The earliest events in development of the mammalian visual system are thought to be independent of electrical activity. In the retinogeniculate pathway, for example, neurogenesis in the retina and lateral geniculate nucleus (LGN), axon outgrowth from the retina along the optic nerve and tract, target recognition, and initial addressing of axon arbors, all occur prenatally, long before visually driven activity exists in the retina [1]. However, subsequent developmental events that also occur before eye-opening and the onset of visual activity nonetheless require neural activity. Neuronal activity is required for the segregation of axons from each eye into eye-specific layers in the LGN of cats and ferrets [2,3], and the subsequent segregation of axons from each eye into on-center and off-center sublayers in ferrets [4]. Although these events occur before visually driven electrical activity, spontaneous or background electrical activity can be recorded from retinal ganglion cells before the onset of vision. Waves of activity in the retina suggest retinotopically patterned activity before photoreceptors are active [5]. A recent study [6•] demonstrated that nearby alpha and gamma retinal ganglion cells are electrically coupled to each other via gap junctions early in development, providing a likely physiological substrate for the pattern of activation. Thus, retinogeniculate axons from the same eye and from similar parts of the retina can have synchronous activity before visually driven activity. In addition, the activity of on-center axons and of off-center axons may be correlated because dendrites of on- and off-center retinal ganglion cells are stratified in the retina; this stratification itself is dependent on activity in at least the on-center pathway [7]. Blocking electrical activity in retinofugal afferents with intrathalamic infusion of tetrodotoxin (TTX) in kittens prevents the segregation of afferents into eye-specific layers [8]; repeated intraocular injections of TTX in ferrets at a slightly later developmental stage prevents the segregation of afferents into 'on' and 'off' sublayers (KS Cramer, M Sur, unpublished observations).

At a still later stage, visually driven afferent activity plays a significant role in sharpening connections in both the LGN and the visual cortex. Blocking retinal activity with intravitreal injection of TTX in postnatal kittens, or reducing activity with lid suture, alters the morphol-

Abbreviations

APV—2-amino-5-phosphonovalerate; **GABA**—γ-aminobutyric acid; **LGN**—lateral geniculate nucleus; **LTD**—long-term depression; **LTP**—long-term potentiation; **NMDA**—*N*-methyl-D-aspartate; **NO**—nitric oxide; **NOS**—NO synthase; **TTX**—tetrodotoxin.

ogy of retinogeniculate axon arbors (reviewed in [9]). Similar manipulations also alter the extent of thalamocortical arbors: arbors related to the deprived or blocked eye shrink, whereas those related to the non-deprived or normal eye remain widespread in cortex [10,11]. Consistent with this broadening of thalamocortical input, cortical cells are physiologically dominated by the non-deprived eye [1,12]. The clustered, horizontal distribution of intracortical axon arbors also develops from an initially random spread and is influenced significantly by lid suture [13,14].

An important variation of the lid suture experiments demonstrates that postsynaptic activity in cortical cells acts together with presynaptic activity to modify the strength of synaptic inputs and the anatomical spread of thalamocortical afferents. When cortical cells are prevented from firing by infusion of muscimol, a $GABA_A$ receptor agonist, their visual responses are dominated by the deprived eye and arbors related to the deprived eye are more widespread in cortex [15,16•]. These experiments argue that activity-dependent refinement of connections is akin to a Hebbian process, mediated by coincident pre- and postsynaptic activity. This idea is supported by other experiments [17–21] that demonstrate the importance of the pattern of afferent activity, rather than the overall amount of activity, in the remodeling and refinement of cortical connections. Artificial strabismus during development disrupts the spatial alignment of activity from the two eyes impinging on single cells in visual cortex, without altering the overall amount of activity. This manipulation causes most cells in cortex to be driven monocularly rather than binocularly, as in normal animals, and ocular dominance columns to be more sharply delineated than normal [17]. A crucial role for temporal patterning of input activity is demonstrated by an experiment in which the optic nerves in kittens were stimulated electrically after blocking retinal activity bilaterally with TTX [18]. Following this manipulation, many more cortical cells were monocularly driven when the two optic nerves were stimulated asynchronously than when they were stimulated synchronously. In another set of experiments, Sur *et al.* [19] induced retinal projections to innervate auditory thalamus in ferrets, so that auditory cortex developed with visual rather than auditory input and hence with a different temporal pattern of input activity than in normal animals. Auditory cortex in 'rewired' ferrets developed orientation- and direction-selective visual receptive fields [20], and a topographic map of visual space [21].

Activity-dependent development and synaptic plasticity: a hypothesis

How might temporally synchronous activation (of two afferents to the same cell) be detected and used to implement a Hebbian process for strengthening synapses from both afferents? One of the mechanisms proposed for a cellular implementation of activity-dependent development is based closely on mechanisms proposed for a form of synaptic plasticity, long-term potentiation (LTP), in the CA1 region of the hippocampus. There are various forms of LTP [22•]; the remodeling of connections in a developing pathway best approximates 'associative LTP', in which paired activation of two inputs to a cell typically results in the strengthening of both inputs (see Fig. 1a). There is substantial evidence that NMDA receptors on CA1 pyramidal cells are necessary for the induction of LTP. They function as detectors of coincident pre- and postsynaptic activation, allowing the entry of Ca^{2+} into the postsynaptic cell. Whereas the induction of LTP is postsynaptic, the maintenance of LTP includes enhanced transmitter release from the presynaptic terminal [23,24]. A retrograde messenger from the postsynaptic cell to the presynaptic terminal is therefore implicated; considerable evidence suggests that nitric oxide (NO), a free radical gas, plays such a role [25–27].

A consequent hypothesis for strengthening synapses or consolidating connections during development is that synchronous activity in afferents activates NMDA receptors on postsynaptic cells, enabling Ca^{2+} to enter these cells (see Fig. 1a). The Ca^{2+} binds calmodulin and activates a nitric oxide synthase (NOS), which produces NO from L-arginine (reviewed in [27–29]). The NO diffuses from the postsynaptic cells to nearby, recently active, terminals, serving to stabilize them. The actual targets of NO activity in the presynaptic terminal are not yet fully understood.

Although considerable evidence supports a critical role for NMDA receptors in synaptic plasticity, it is important to note that some forms of LTP, such as that seen in mossy fibers at CA3 pyramidal cells [30,31], do not require activation of NMDA receptors. The role of NO as a retrograde messenger is also disputed. In some studies, NOS inhibitors do not prevent the formation of LTP with specific stimulation paradigms [32]; NOS inhibitors may even promote LTP under certain conditions [32,33]. Other retrograde messengers have been proposed, including arachidonic acid, platelet-activating factor, and carbon monoxide (see [34] for review); no retrograde messenger may be required if LTP is initiated and maintained with postsynaptic mechanisms alone [35]. Still, a mechanism for correlation-based synaptic development is implicated by the evidence for activity-dependent remodeling in the visual system, in which anatomical evidence demonstrates presynaptic changes in response to alterations in the levels and patterns of neuronal activity.

Whereas correlated activity leads to strengthening of synapses, uncorrelated activity may lead to weakening and elimination of synapses. A mechanism for such synaptic weakening may be similar to another form of synaptic plasticity, long-term depression (LTD). Several forms of LTD have recently been identified in the hippocampus, cortex and cerebellum [22•]. A common requirement for homosynaptic LTD, including LTD in visual cortex, is low-frequency afferent activation [36,37];

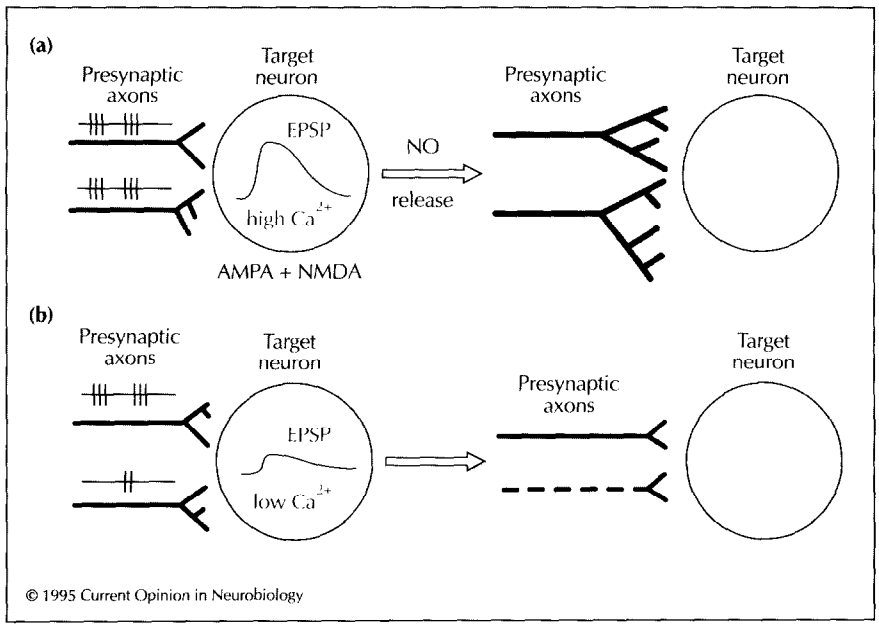

Fig. 1. Possible mechanisms that act during development to increase or decrease synaptic connections between presynaptic axons and target neurons. The figure depicts two axons contacting a cell. Afferent spike activity in the two axons is represented by spike trains above each axon. Excitatory postsynaptic potentials (EPSPs) and Ca^{2+} transients are depicted inside each target neuron. **(a)** Synchronously active axons would consolidate or increase their contacts, via a mechanism similar to associative LTP. **(b)** Asynchronously active axons would have their synapses weakened and decrease their contacts, via a mechanism similar to associative LTD. Whether or not a retrograde messenger such as NO is involved in this process remains unknown. See text for details. Abbreviation: AMPA, α-amino-3-hydroxy-5-methyl isoxazole-4-propionic acid.

heterosynaptic and associative LTD appear to involve asynchronous or out-of-phase stimulation (Fig. 1b). Although NMDA receptors are implicated in certain forms of LTD [37], the important variable for initiating LTD or LTP might be postsynaptic Ca^{2+}: low levels of Ca^{2+} entry trigger LTD, whereas high levels of Ca^{2+} trigger LTP [38] (Fig. 1). A retrograde messenger for reducing synaptic transmission following LTD has been recently demonstrated in the CA1 region of hippocampus [39], and a role for NO has been suggested in cerebellar LTD (see [27] for review).

Many questions remain about an LTD-like mechanism and an associated retrograde messenger during development. The messenger associated with uncorrelated activity might act on a different substrate than that associated with correlated activity. Given the low spike rates of retinal ganglion cells, at least early in development [40], an interesting possibility is that the 'default' mechanism for activity-dependent development is in fact similar to LTD and results in the removal of exuberant synapses and connections.

There is strong evidence that NMDA receptors are involved in specific developmental events in the mammalian visual pathway, and some evidence for a role for NO. (However, NMDA receptors appear not to be involved in some aspects of development, just as there is evidence for non-NMDA forms of LTP in specific parts of the hippocampus.) The feasibility of forming appropriate projections on the basis of a diffusible retrograde messenger with a short half-life, such as NO, has been demonstrated using computer simulations [41]. In the following section, we review recent experiments that address the comparison with LTP and LTD, by testing the roles of NMDA receptors and NO in activity-dependent remodeling during development.

The role of NMDA receptors

NMDA receptor activation is required for refinement of projections in several regions of the developing visual system. Cline and Constantine-Paton [42] first demonstrated that blocking NMDA receptors in the frog optic tectum disrupted the segregation of eye-specific stripes induced by a supernumerary (third) eye. In the mammalian thalamus, NMDA receptor blockade disrupts the segregation of on- and off-center retinogeniculate afferents into sublayers in ferrets [4]. Individual axon arbors remain either abnormally large, or are reduced in size but inappropriately located within the LGN. Recent studies have shown that NMDA receptors are present on LGN cells during development [43,44]. Moreover, developing LGN cells show NMDA-dependent LTP [45••], suggesting that the mechanisms for both synaptic plasticity and activity-dependent refinement of connections are present simultaneously. In the superior colliculus of rats, Simon *et al.* [46] have shown that the NMDA receptor is required for the refinement of topography in the retino-collicular projection. This refinement can involve removal of large portions of axonal branches. In the cat visual cortex, NMDA receptors are present during the critical period for refining thalamocortical connections [47]. Blocking these receptors prevents the ocular dominance shift that occurs after monocular lid suture [48]. In other systems, mice lacking NMDA receptors have been shown to lack barrelettes, or whisker-related patterns in the brainstem [49•]. In the barrel fields (whisker representations) of rat somatosensory cortex, NMDA receptor blockade does not interfere with the formation of barrels in normal development, but does interfere with remodeling of connections following experimental removal of whiskers [50•].

NMDA receptors may influence development by shaping the structure of postsynaptic neurons and putative synaptic sites. Infusion of 2-amino-5-phosphonovalerate (APV), an NMDA receptor antagonist, into the ferret LGN during the period of retinogeniculate axon remodeling results in significantly greater branching and numbers of spines on LGN cells (M Rocha, A Ramoa, J Hahm, M Sur, Soc Neurosci Abstr 1991, 17:1136; M Rocha, M Sur, unpublished data). In addition, in acute slices observed at several timepoints with confocal imaging, application of APV results in a rapid increase in the rate of addition of dendritic spines (M Rocha, M Sur, Soc Neurosci Abstr 1994, 20:1417). In the cat LGN, infusion of TTX also leads to an increase in the number of dendritic spines on LGN cell dendrites [51]. Thus, blocking activity, in general, and NMDA receptors in particular, may cause cells to upregulate postsynaptic sites, in concert with upregulation of presynaptic branching and contacts.

Some activity-mediated remodeling of projections does not seem to require activation of NMDA receptors. In the formation of eye-specific layers in the ferret LGN, chronic application of NMDA receptor antagonists does not disrupt the normal pattern [52•]. In the cat, this segregation is disrupted with application of TTX [8]. Thus, the removal of portions of axon arbors from inappropriate layers (and elaboration of terminal arbors in appropriate layers) relies on afferent neuronal activity but is mediated independently of the NMDA receptor. Remodeling of retinogeniculate axons into eye-specific layers may thus rely on activity through non-NMDA receptors, or perhaps on activation of voltage-gated Ca^{2+} channels on postsynaptic neurons.

A role for nitric oxide

Whether or not NO is involved in the developmental refinement of connections has been tested directly in recent experiments. In the developing chick retinotectal projection, NOS expression coincides with removal of a transient ipsilateral projection [53]. Blockade of NOS prevents removal of this transient projection [54•]. It is not clear whether removal of this transient ipsilateral projection requires NMDA receptor activation. However, in the ferret LGN, NOS, revealed using NADPH-diaphorase histochemistry, is transiently expressed during early postnatal development, at a period coinciding with segregation of retinal ganglion cell inputs into sublaminae [55]. When NOS is blocked systemically during the third and fourth postnatal weeks using arginine analogs, sublamination is disrupted (KS Cramer, M Sur, Soc Neurosci Abstr 1994, 20:1470). In the ferret's retinogeniculate pathway, NMDA receptors are known to be present and involved in refining connections; thus, NO may act downstream of the NMDA receptor in refining this projection. In the cat visual cortex, however, blockade of NOS does not appear to disrupt formation of ocular dominance columns (DC Gillespie *et al.*, Soc Neurosci Abstr 1993, 19:893). In this system, it is possible that a different retrograde messenger effects developmental changes following NMDA receptor activation.

Conclusions

Neuronal activity is required for fine-tuning projections in the visual system after an initial, more diffuse projection is made. This activity can arise from visual responses or from spontaneous activity in retinal ganglion cells. Activity-dependent remodeling reflects the fact that afferents that have correlated activity will strengthen their synapses on a target cell, whereas afferents with uncorrelated or asynchronous activity would have their synapses weakened.

The requirement for synaptic activity through NMDA receptors has been demonstrated in several, but not all, aspects of refinement in the developing visual system. The requirement for NMDA receptor activation is similar to that seen in certain forms of synaptic plasticity in the hippocampus. Insights into the mechanisms by which NMDA receptors are involved in refinement of connections can be gained from the recent interest in retrograde messengers in LTP; both systems require a post- to presynaptic retrograde messenger in order to effect synaptic changes. Recent experiments suggest that NO has a role in the refinement of at least some projections in the developing visual system. While the mechanisms underlying synaptic plasticity are far from resolved, and the role of NO in hippocampal LTP remains controversial, it has been instructive to examine the roles of NMDA receptors and NO in the context of development. In the future, it will also be of interest to investigate other postulated mechanisms for detecting correlated afferent activity and transmitting retrograde signals, in both synaptic plasticity and activity-dependent refinement of connections.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Goodman CS, Shatz CJ: **Developmental mechanisms that generate precise patterns of neuronal connectivity.** *Cell* 1993, **10(suppl)**:77–98.

2. Shatz CJ: **The prenatal development of the cat's retinogeniculate pathway.** *J Neurosci* 1983, **3**:482–499.

3. Linden DC, Guillery RW, Cucchiaro J: **The dorsal lateral geniculate nucleus of the normal ferret and its postnatal development.** *J Comp Neurol* 1981, **203**:189–211.

4. Hahm J-O, Langdon RB, Sur M: **Disruption of retinogeniculate afferent segregation by antagonists to NMDA receptors.** *Nature* 1991, **351**:568–570.

5. Meister M, Wong ROL, Baylor DA, Shatz CJ: **Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina.** *Science* 1991, **252**:939–943.

6. • Penn AA, Wong ROL, Shatz CJ: **Neuronal coupling in the developing mammalian retina.** *J Neurosci* 1994, **14**:3805–3815.
In this study, the presence of gap junctions was inferred using dye coupling following intracellular injections in the ferret retina. The authors demonstrate coupling between alpha and gamma retinal ganglion cells, and its developmental time course.

7. Bodnarenko SR, Chalupa LM: **Stratification of ON and OFF ganglion cell dendrites depends on glutamate-mediated afferent activity in the developing retina.** *Nature* 1993, **364**:144–146.

8. Shatz CJ, Stryker MP: **Prenatal tetrodotoxin infusion blocks segregation of retinogeniculate afferents.** *Science* 1988, **242**:87–89.

9. Garraghty PE, Sur M: **Competitive interactions influencing the development of retinal axonal arbors in cat lateral geniculate nucleus.** *Physiol Rev* 1993, **73**:529–545.

10. Antonini A, Stryker MP: **Development of individual geniculocortical arbors in cat striate cortex and effects of binocular impulse blockade.** *J Neurosci* 1993, **13**:3549–3573.

11. Antonini A, Stryker MP: **Rapid remodeling of axonal arbors in the visual cortex.** *Science* 1993, **260**:1819–1821.

12. Shatz CJ: **Impulse activity and the patterning of connections during CNS development.** *Neuron* 1990, **5**:745–756.

13. Callaway EM, Katz LC: **Emergence and refinement of clustered horizontal connections in cat striate cortex.** *J Neurosci* 1990, **10**:1134–1153.

14. Callaway EM, Katz LC: **Effects of binocular deprivation on the development of clustered horizontal connections in cat striate cortex.** *Proc Natl Acad Sci USA* 1991, **88**:745–749.

15. Reiter HO, Stryker MP: **Neural plasticity without postsynaptic action potentials: less-active inputs become dominant when kitten visual cortical cells are pharmacologically inhibited.** *Proc Natl Acad Sci USA* 1988, **85**:3623–3627.

16. • Hata Y, Stryker MP: **Control of thalamocortical afferent rearrangement by postsynaptic activity in developing visual cortex.** *Science* 1994, **265**:1732–1735.
This paper provides an anatomical demonstration that arbors of axons related to the sutured eye in kittens expand their cortical territory when postsynaptic cortical cells are prevented from firing action potentials resulting from an intracortical infusion of muscimol, a $GABA_A$ receptor agonist.

17. Lowel S, Singer W: **Monocularly induced 2-deoxyglucose patterns in the visual cortex and lateral geniculate nucleus of the cat: II. Awake animals and strabismic animals.** *Eur J Neurosci* 1993, **5**:857–869.

18. Stryker MP, Strickland SL: **Physiological segregation of ocular dominance columns depends on the pattern of afferent electrical activity.** *Invest Ophthalmol Vis Sci* 1984, **25 (suppl)**:278.

19. Sur M, Garraghty PE, Roe AW: **Experimentally induced visual projections into auditory thalamus and cortex.** *Science* 1988, **242**:1437–1441.

20. Roe AW, Pallas SL, Kwon YH, Sur M: **Visual projections routed to the auditory pathway in ferrets: receptive fields of visual neurons in primary auditory cortex.** *J Neurosci* 1992, **12**:3651–3664.

21. Roe AW, Pallas SL, Hahm J-O, Sur M: **A map of visual space induced into primary auditory cortex.** *Science* 1990, **250**:818–820.

22. • Linden DJ: **Long-term synaptic depression in the mammalian brain.** *Neuron* 1994, **12**:457–472.
An up-to-date review of the literature on long-term depression (LTD) in the mammalian hippocampus, cerebellum, and cerebral cortex, and of issues concerning long-term potentiation (LTP).

23. Bekkers JM, Stevens CF: **Presynaptic mechanism for long-term potentiation in the hippocampus.** *Nature* 1990, **346**:724–729.

24. Malinow R, Tsien RW: **Presynaptic enhancement shown by whole-cell recordings of long-term potentiation in hippocampal slices.** *Nature* 1990, **346**:177–180.

25. Schuman EM, Madison DV: **A requirement for the intercellular messenger nitric oxide in long-term potentiation.** *Science* 1991, **254**:1503–1506.

26. O'Dell TJ, Hawkins RD, Kandel ER, Arancio O: **Tests of the roles of two diffusible substances in long-term potentiation: evidence for nitric oxide as a possible early retrograde messenger.** *Proc Natl Acad Sci USA* 1991, **88**:11285–11289.

27. Schuman EM, Madison DV: **Nitric oxide and synaptic function.** *Annu Rev Neurosci* 1994, **17**:153–183.

28. Bredt DS, Snyder SH: **Nitric oxide, a novel neuronal messenger.** *Neuron* 1992, **8**:3–11.

29. Dawson TM, Snyder SH: **Gases as biological messengers: nitric oxide and carbon monoxide in the brain.** *J Neurosci* 1994, **14**:5147–5159.

30. Harris EW, Cotman CW: **Long-term potentiation of guinea pig mossy fiber responses is not blocked by *N*-methyl-D-aspartate antagonists.** *Neurosci Lett* 1986, **70**:132–137.

31. Weisskopf MG, Castillo PE, Zalutsky RA, Nicoll RA: **Mediation of hippocampal mossy fiber long-term potentiation by cyclic AMP.** *Science* 1994, **265**:1878–1882.

32. Gribkoff VK, Lum-Ragan JT: **Evidence for nitric oxide synthase inhibitor-sensitive and insensitive hippocampal synaptic potentiation.** *J Neurophysiol* 1992, **68**:639–642.

33. Izumi Y, Clifford DB, Zorumski CF: **Inhibition of long-term potentiation by NMDA-mediated nitric oxide release.** *Science* 1993, **257**:1273–1276.

34. Williams JH, Errington ML, Li Y-G, Lynch MA, Bliss TVP: **The search for retrograde messengers in long-term potentiation.** *Semin Neurosci* 1993, **5**:149–158.

35. Manabe T, Nicoll RA: **Long-term potentiation: evidence against an increase in transmitter release probability in the CA1 region of the hippocampus.** *Science* 1994, **265**:1888–1892.

36. Kirkwood A, Bear MF: **Homosynaptic long-term depression in the visual cortex.** *J Neurosci* 1994, **14**:3404–3412.

37. Kirkwood A, Dudek SM, Gold JT, Aizenman CD, Bear MF: **Common forms of synaptic plasticity in the hippocampus and neocortex *in vitro*.** *Science* 1993, **260**:1518–1521.

38. Artola A, Singer W: **Long-term depression of excitatory synaptic transmission and its relationship to long-term potentiation.** *Trends Neurosci* 1993, **16**:480–487.

39. Bolshakov VY, Siegelbaum SA: **Postsynaptic induction and presynaptic expression of hippocampal long-term depression.** *Science* 1994, **264**:1148–1152.

40. Galli L, Maffei L: **Spontaneous impulse activity of rat retinal ganglion cells in prenatal life.** *Science* 1988, **242**:90–91.

41. Montague PR, Gally JA, Edelman GM: **Spatial signaling in the development and function of neural connections.** *Cereb Cortex* 1991, **1**:199–220.

42. Cline HT, Constantine-Paton M: **NMDA receptor antagonists disrupt the retinotectal topographic map.** *Neuron* 1989, **3**:413–426.

43. White CA, Sur M: **Membrane and synaptic properties of developing lateral geniculate nucleus neurons during retino-**

geniculate axon segregation. *Proc Natl Acad Sci USA* 1992, **89**:9850–9854.

44. Ramoa AS, McCormick DA: **Enhanced activation of NMDA receptor responses at the immature retinogeniculate synapse.** *J Neurosci* 1994, **14**:2098–2105.

45. •• Mooney R, Madison DV, Shatz CJ: **Enhancement of transmission at the developing retinogeniculate synapse.** *Neuron* 1993, **10**:815–825.
In this study, the physiology of the developing lateral geniculate nucleus was examined using the acute slice preparation. This paper provides the first evidence for NMDA-mediated LTP in the lateral geniculate nucleus during development.

46. Simon DK, Prusky GT, O'Leary DDM, Constantine-Paton M: **N-methyl-D-aspartate receptor antagonists disrupt the formation of a mammalian neural map.** *Proc Natl Acad Sci USA* 1992, **89**:10593–10597.

47. Fox K, Sato H, Daw NW: **The location and function of NMDA receptors in cat and kitten visual cortex.** *J Neurosci* 1989, **9**:2443–2454.

48. Bear MF, Kleinschmidt A, Gu Q, Singer W: **Disruption of experience-dependent synaptic modifications in striate cortex by infusion of an NMDA receptor antagonist.** *J Neurosci* 1990, **10**:909–925.

49. • Li Y, Erzurumlu RS, Chen C, Jhaveri S, Tonegawa S: **Whisker-related neuronal patterns fail to develop in the trigeminal brainstem nuclei of NMDAR1 knockout mice.** *Cell* 1994, **76**:427–437.
The authors demonstrate that the brains of mice lacking a gene for an NMDA receptor subtype have defective patterns of development, consistent with a role for this receptor in pattern formation in normal animals.

50. • Schlaggar BL, Fox K, O'Leary DDM: **Postsynaptic control of plasticity in developing somatosensory cortex.** *Nature* 1993, **364**:623–626.
Blockade of NMDA receptors disrupts plasticity in the cortical barrel fields, but apparently does not interfere with normal pattern formation.

51. Dalva MB, Ghosh A, Shatz CJ: **Independent control of dendritic and axonal form in the developing lateral geniculate nucleus.** *J Neurosci* 1994, **14**:3588–3602.

52. • Smetters DK, Hahm J-O, Sur M: **An *N*-methyl-D-aspartate receptor antagonist does not prevent eye-specific segregation in the ferret retinogeniculate pathway.** *Brain Res* 1994, **658**:168–178.
The authors present an important exception in visual system development: they demonstrate that NMDA receptors do not have a role in the segregation of retinogeniculate arbors into eye-specific layers. Thus, the mechanism underlying this type of segregation differs from the NMDA receptor-dependent segregation of retinogeniculate axons into sublaminae later in development.

53. Williams CV, Nordquist D, McLoon SC: **Correlation of nitric oxide synthase expression with changing patterns of axonal projections in the developing visual system.** *J Neurosci* 1994, **14**:1746–1755.

54. • Wu HH, Williams CV, McLoon SC: **Involvement of nitric oxide in the elimination of a transient retinotectal projection in development.** *Science* 1994, **265**:1593–1596.
When nitric oxide synthase was blocked using arginine analogs, the transient ipsilateral projection in the developing chick retinotectal projection was retained. This finding demonstrates a role for nitric oxide in the removal of transient projections in development.

55. Cramer KS, Moore CI, Sur M: **Transient expression of NADPH-diaphorase in the lateral geniculate nucleus of the ferret during early postnatal development.** *J Comp Neurol* 1995:in press.

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