

Neuronal activity during development: permissive or instructive?

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Experimental studies over the past year have shown that neural activity has a range of effects on the development of neural pathways. Although activity appears unimportant for establishing many aspects of the gross morphology and topology of the brain, there are many cases where the presence of neural activity is essential for the formation of a mature system of neural connections; in some instances, the pattern of neural activity actually orchestrates the final arrangement of neural connections.

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Abbreviations

APV	2-amino-5-phosphonopentanoic acid
GABA	γ -aminobutyric acid
NMDA	<i>N</i> -methyl-D-aspartate
TTX	tetrodotoxin

Introduction

Some aspects of neural circuit development require neural activity to perform with precision. A classic example is the development of ocular dominance columns in visual cortex, which fail to form in the absence of afferent activity arriving from the eyes [1–3]. What remains uncertain is whether the role of neural activity in development is instructive or permissive. In other words, it is not clear whether the pattern of neural activity molds directly the development of the neural connections or whether it is simply the presence of neural activity that enables other developmental cues, such as molecular factors, to guide appropriate neural connections. This review will examine progress over the past year toward distinguishing between an instructive and a permissive role for neural activity in the development of brain circuits. Recent evidence regarding putative cellular and synaptic mechanisms by which neural activity might influence the development of neural circuits will also be discussed.

How can one distinguish between permissive and instructional roles for activity?

The most direct and informative way to distinguish between instructive and permissive roles for neural activity is to change the pattern or information content of the neural activity, while keeping the overall activity constant, and see whether and how this affects the development of neural circuits. The expectation is that different patterns of afferent activity will ‘teach’ or reinforce a different arrangement of connections, perhaps using a competitive mechanism that executes a form of Hebbian learning [4,5]. This type of manipulation is difficult to execute, but the

existing evidence indicates that, at least in some circuits, changes in the statistical pattern of neural activity can lead to profound differences in the final arrangement of neural connections [6]. These experiments showed that inducing artificial, synchronized activity between the eyes, while simultaneously silencing intrinsic activity, abolished the pattern of eye preference domains (i.e. ocular dominance columns) in the cortex. The ocular dominance columns were preserved if the artificial stimulation was of the same frequency but asynchronous between the eyes. This is just what one would expect if ocular dominance columns develop through a competitive process that selects for presynaptic afferents that are most capable of driving responses in postsynaptic cells. This Hebbian correlation mechanism predicts that the synchronously active (stimulated) presynaptic fibers in both eyes will not segregate, but that asynchronous activation will lead to segregation.

More recently, Weliky and Katz [7•] analyzed the effects of artificial optic nerve stimulation on the development of orientation domains in the visual cortex. They found that artificial stimuli, together with whatever spontaneous neural activity normally exists in the optic nerve, reduces the orientation selectivity and responsiveness of visual cortical neurons. This decrement is reminiscent of the effects of prolonged binocular deprivation [2]. These experiments imply that the artificially supplied electrical stimulation inhibits the normal development of orientation maps, perhaps by interfering with the effects of spontaneous activity.

Spontaneous neural activity during development

Short of a way to substitute for spontaneous activity with artificially induced stimuli, many experimenters have instead explored the effects of simply interfering with spontaneous activity on the development of neural connections. For instance, spontaneous waves of neural activity in the retina, which are present during the development of the visual pathways even before eye opening [8,9], were recently shown to be necessary for the formation of eye-specific laminae in the ferret lateral geniculate nucleus [10•]. These experiments show that if the spontaneous retinal waves, along with the resultant action potentials in retinal ganglion cells, are blocked pharmacologically, eye-specific laminae fail to form. This manipulation specifically blocked the afferent neural activity generated in the eyes, unlike previous experiments that yielded similar results but blocked both the pre- and postsynaptic activity of the retinal ganglion cells and geniculate cells [11].

The sublaminar organization of the ferret geniculate into ON/OFF domains, which takes place after the development of eye-specific laminae, has also recently been shown to rely on afferent neural activity [12•]. Taken

together, these experiments provide compelling evidence that afferent neural activity is at least permissive for the formation of an adult-like pattern of neural connections in the retino-geniculate pathway. Further experiments that could alter or decorrelate the spontaneous retinal activity, rather than eliminate it all together, are necessary to definitively distinguish whether the activity is instructive or simply permissive.

It is easy to understand how spontaneous waves of retinal activity can help establish eye-specific laminae in the geniculate, because the waves are independent in the two eyes. Experiments investigating how patterns of spontaneous activity in the retina might also lead to the formation of ON/OFF sublaminae in the geniculate have revealed that OFF ganglion cells burst much more often than ON cells [13]. This difference in spontaneous activity may be attributable to the distinct effects of GABAergic inhibition on the two classes of retinal ganglion cells [14•], and is theoretically sufficient to cause the segregation of ON and OFF laminae observed in the geniculate [15].

Further evidence supporting an instructive role for spontaneous afferent activity in patterning of retino-geniculate connections comes from experiments in which afferents from the eye were experimentally induced to form connections in auditory thalamus that had previously been denervated [16•]. These retino-auditory thalamus axons do not induce the formation of large eye-specific domains, such as the laminae in visual thalamus, but they do form eye-specific clusters on a smaller scale. This is consistent with spontaneous retinal activity instructing eye-specific afferents to cluster in an ‘unnatural’ target, the auditory thalamus; however, the role of spontaneous activity in the clustering process was not tested directly in this study.

Recent experiments, whose results are in agreement with those of classic studies [2,17••], show definitively that patterned visual experience is not necessary for the development of either ocular dominance or orientation maps, even at the level of detailed matching of orientation preference between the two eyes [18,19••]. This means that the instructional nature of neural activity, if it is in fact imperative, can take the form of patterns of spontaneous activity during development. This is an important distinction that is sometimes lost: neural activity acting in an instructive way does not necessarily require sensory experience as the spontaneous pattern of neural activity in a developing circuit can itself be instructive. These spontaneous neural activity patterns, acting through a competitive mechanism, are theoretically sufficient to lead to the development of orientation and ocular dominance maps in the cortex [20]. However, to form matching orientation maps between the eyes in the absence of visual experience [19••], patterns of correlated spontaneous activity must exist across the laminae in the geniculate representing both eyes, and these correlations must differentiate between centre-type (ON or OFF) cells [20]. Simple differences in mean activities of ON versus

OFF cells would not be sufficient — there must be a component of cross-laminae correlations that is reasonably localized and center-type specific. Such patterns of correlated spontaneous activity have not yet been reported.

Neural activity in developmental plasticity

The difficulty with directly interfering in the early development of neural connection patterns (because of the fragility of young animals) has led many researchers to alternative experimental approaches. The most common of these is to induce plasticity in partially developed circuits, and then test the role of activity in mediating developmental plasticity. Whether or not the *de novo* construction of the pattern of neural connections requires instruction from activity is a different question than whether activity can change the pattern of existing but still developing circuits. Nevertheless, in so far as plasticity and *de novo* construction follow the same or similar rules, these plasticity experiments can be revealing about the role of neural activity in the development of brain circuits.

Wiesel and Hubel [21] originally followed this alternative approach in cats by covering one eye during development, thereby changing the fundamental character of their visual experience. This intervention causes profound changes in the neural circuit that is brought into adulthood, inducing most cells to respond to the open eye and leaving few cells to respond to the closed eye, with the most profound effects caused by the earliest deprivations [22•]. The cells that do remain responsive to the closed eye have receptive field characteristics that reflect their limited visual experience — they have very poor selectivity for stimulus orientation and respond well to full field stimuli [2,23•]. These are precisely the characteristics of the remaining visual stimulation through the closed eyelid. Moreover, the deprived-eye-responsive cells cluster together into tight groups, perhaps as a way to better compete for cortical territory against afferents from the remaining open eye.

More direct evidence of neural activity mediating a competitive process in developmental plasticity comes from experiments in which the postsynaptic cell is inhibited pharmacologically. In these cases, the visual cortex responds better to the closed eye in the area of visual cortex that is inhibited [24]. This is precisely what one would predict should happen if there is a Hebbian competition for cortical target space among the thalamocortical afferents serving the two eyes. In this scenario, activity in the afferents serving the closed eye is more strongly correlated with activity in the cortex (both are reduced) than is activity in the open eye afferents, which remains robust.

Another manipulation that has been effectively used to test the mechanisms of developmental plasticity is visual squint or strabismus. Inducing strabismus during development, which decorrelates the pattern of visually driven activity in the two eyes, changes the pattern of ocular dominance columns [25,26] and causes cells to

respond more monocularly [21]. This sharpening of eye preference is expected if visually driven neural activity is shaping the development of thalamocortical afferents into eye-specific domains in the cortex. In addition, the pattern of cortico-cortical connections [27] and callosal connections [28•] is altered in strabismic cats. In cats with normal visual experience, cortico-cortical connections (both inter- and intra-hemispheric) link like orientation columns, but are not eye specific. In strabismic cats, these connections become both eye specific and orientation specific, presumably because of the correlation properties of the visual experience. Note also that in the absence of cortical activity, the cortico-cortical connections would not cluster at all [29]. These findings imply that neural activity is at least permissive, and may be instructive, in determining the arrangement of cortico-cortical connections in visual cortex.

The amphibian retino-tectal system

In the amphibian visual system, manipulation and observation of the development of the retino-tectal pathway is relatively simple, and many close analogies with the development of mammalian vision can be inferred. For example, the optic tectum normally receives input directly from the contralateral eye only, but can be induced to receive inputs from an ectopic third eye. The doubly innervated tectum then develops eye-preference domains (a.k.a. ocular dominance ‘stripes’) in an activity-dependent manner that closely resembles the mammalian visual system [30]. These analogies make retino-tectal development a very useful model system for characterizing the role of activity in the development of neural connectivity patterns [31]. Recent experiments in this system have demonstrated that synchronized retinal activity produced by strobe rearing applied to both eyes disrupts the development of the binocular map in the optic tectum [32•]. These results suggest that activity is instructive in the development of the tectal retinotopic map, not just permissive.

Mechanisms for activity-dependent neural circuit development

An alternative approach to investigating the role of activity in neural circuit development is to interfere with the cellular mechanisms mediating activity-dependent development, without interfering with the activity itself. Changing the ‘instruction’ by modulating the ‘message’ may provide insights into both the mechanism and the message. The NMDA receptor, for the same reasons that it is implicated in learning and memory processes, is a prominent candidate to mediate activity-dependent development. This is because the inherent voltage-dependent biophysical properties of the receptor make it act like a correlator for pre- and postsynaptic activity, and therefore, it is a natural synaptic operator for Hebbian correlations.

Significant progress has been made in determining whether and how NMDA receptor mediated activity might instruct neural circuit development. It has recently been shown that

visual experience and neural activity can regulate the expression of the NMDA R1 subunit of the NMDA receptor in cats and ferrets [33•,34•]. Moreover, chronic treatment of optic tectum with NMDA, which has been shown to block activity-dependent refinement [35], has now been shown to decrease NMDA-receptor-mediated currents [36]. This suggests that neural activity acting through the NMDA receptor regulates activity-dependent neural circuit development. One mechanism for this regulation may be through the expression of different NMDA receptor subtypes, because they have ionic conductances with distinct amplitudes and duration, which can make them variably permissive for synaptic plasticity [37]. Moreover, these NMDA currents [37–39] and the receptor subtypes [40••] are regulated during development. This could provide a direct means to control activity-dependent plasticity.

One of the major difficulties with these and previous attempts [41] to distinguish between an instructive and a permissive role of NMDA receptor mediated activity in development has been that blockade of NMDA receptors can also significantly reduce overall activity [42]. More recent experiments have revisited this problem using a molecular approach by infusing antisense oligonucleotides *in vivo* to reduce the expression of the NMDA receptor in visual cortical cells [43••]. The results of these experiments suggested that the level of NMDA-mediated activity can be modulated in a way that blocks plasticity but does not interfere with visually driven activity. This finding strongly supports NMDA in the mediation of activity-dependent plasticity, acting in an instructive capacity.

Rodent barrel field experiments

The development of some brain structures, particularly early in the establishment of neural pathways, is not directly regulated by neural activity. For example, procedures in which tetrodotoxin (TTX) is applied to essentially the entire brain cavity early in development have resulted in no gross morphological defects in the development of the forebrain and thalamic structures, even though eye-specific laminae in the geniculate nucleus fail to form [11]. These results and those of other experiments have led to the general belief that early axon pathfinding and the establishment of gross topographic maps are processes that do not rely on neural activity [44]. However, recent experiments suggest that some aspects of axon pathfinding may be activity dependent [45•,46•]. These experiments show that, in the presence of TTX, thalamocortical afferents and intracortical axons either fail to find their normal target territory or form synapses nonspecifically in incorrect locations. This implies that even some early aspects of neural circuit formation, such as axon branching and pathfinding, may be activity dependent.

The potentially precocious role of activity in axon pathfinding is in contrast to experimental results in the somatosensory cortex, where activity appears to play no role in the establishment of a somatotopic map, or even in the formation of

the morphological 'barrel' field in rodents [47]. Activity does, however, appear to be important for some aspects of barrel field plasticity [48] and for the 'one-to-one' mapping of the physiological response of cortical barrel field neurons to whisker stimulation [49]. For instance, barrel field plasticity is partially blocked by the application of APV, the potent NMDA receptor antagonist [48]. Moreover, mice lacking the NMDAR1 subunit, which is essential for NMDA receptor function, have abnormal somatotopic patterning in the brainstem trigeminal nucleus [50]. Unfortunately, these NMDAR1 knockout mice die soon after birth, too early to tell whether the development of the cortical barrel field is also abnormal.

Recent experiments in which NMDA receptor function has been partially or fully rescued via the ectopic expression of an NMDAR1 transgene in NMDAR1 knockout mice have shed considerably more light on the role of NMDA receptors in barrel field formation [51••]. The NMDAR1 knockout mice that have been only partially rescued with low levels of the NMDAR1 transgene live for several weeks, but still do not have morphological barrels in the trigeminal pathway. Mice that have been rescued with high levels of the transgene have a normal somatotopic map with barrels. These experiments suggest that NMDA receptor activation, possibly spontaneous, is also essential for barrel field development. It remains a mystery why blocking action potentials with TTX has no effect on barrel field morphology but removing NMDA receptors prevents the formation of barrels.

Conclusions

Neural activity is not required for the development of the adult arrangement of all neural connections in the brain. As discussed here, however, there are many instances in which the presence, and perhaps even the pattern, of neural activity is necessary for the formation of precise neural connections. The diversity of apparent effects of neural activity on brain circuit formation may simply define a continuum. This ranges from one extreme, at which neural activity is not at all necessary for the establishment of correct neural connections, passes through a permissive role for activity, and then, at the other extreme, the pattern of neural activity instructs the development of neural circuits. Where the development of a particular neural circuit lies in this continuum probably depends on a number of factors, including the presence of neural activity in the developing neurons, the particular stage of development involved, and whether there is competition between different pools of neurons for postsynaptic target territory. Developmental plasticity of neural circuits is a competitive process, and thus typically uses neural activity in an instructive way. In so far as the circumstances for development and plasticity are the same (including competition), they are likely to share common mechanisms. Experiments over the past year have led to considerable advances in our understanding of the mechanisms and the messages for the activity-dependent development of neural circuits.

Acknowledgements

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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. Stryker MP, Harris WA: **Binocular impulse blockade prevents the formation of ocular dominance columns in cat visual cortex.** *J Neurosci* 1986, **6**:2117-2133.
 2. Movshon JA, Kiorpes L: **The role of experience in visual development.** In *Development of Sensory Systems in Mammals*. Edited by Coleman JR. New York: John Wiley & Sons, Inc; 1990:155-202.
 3. Katz LC, Shatz CJ: **Synaptic activity and the construction of cortical circuits.** *Science* 1996, **274**:1133-1138.
 4. Hebb DO: *The Organization of Behavior*. New York: John Wiley & Sons; 1949.
 5. Stent GS: **A physiological mechanism for Hebb's postulate of learning.** *Proc Natl Acad Sci USA* 1971, **70**:997-1001.
 6. Stryker MP, Strickland SL: **Physiological segregation of ocular dominance columns depends on the pattern of afferent electrical activity.** *Invest Ophthalmol Vis Sci* 1984, **25**:278.
 7. Weliky M, Katz LC: **Disruption of orientation tuning in visual cortex**
 - **by artificially correlated neuronal activity.** *Nature* 1997, **386**:680-685.

Artificial electrical stimulation generated with microcuffs implanted around the optic nerve without blockade of action potentials decreases orientation selectivity and responsivity of neurons in ferret visual cortex. Threshold stimulation of the optic nerve did not begin until around the time of normal eye opening and only shortly before orientation maps normally form. The nerve cuffs were implanted around only one optic nerve, the other eye was enucleated. These experiments are consistent with an instructive role for activity in the development of orientation maps.
 8. Maffei L, Galli-Resta L: **Correlation in the discharges of neighboring rat retinal ganglion cells during prenatal life.** *Proc Natl Acad Sci USA* 1990, **87**:2861-2864.
 9. Meister M, Wong RO, Baylor DA, Shatz CJ: **Synchronous bursts of action potentials in ganglion cells of the developing mammalian retina.** *Science* 1991, **252**:939-943.
 10. Penn AA, Riquelme PA, Feller MB, Shatz CJ: **Competition in retinogeniculate patterning driven by spontaneous activity.** *Science* 1998, **279**:2108-2112.
- Blockade of spontaneous retinal waves by the application of various nicotinic acetylcholine receptor (nAChR) agonists (epibatidine) and antagonists (nereis-toxin [NTX]) to both eyes is shown to prevent the formation of eye-specific laminae in the ferret. These pharmacological manipulations block all retinal ganglion cell action potentials as well. Hence, we cannot conclude from these experiments whether or not retinal activity is instructive or permissive, only that it is necessary.
11. Shatz CJ, Stryker MP: **Prenatal tetrodotoxin infusion blocks segregation of retinogeniculate afferents.** *Science* 1988, **242**:87-89.
 12. Cramer KS, Sur M: **Blockade of afferent impulse activity disrupts on/off sublamination in the ferret lateral geniculate nucleus.** *Brain Res Dev Brain Res* 1997, **98**:287-290.
- The development of ON/OFF sublamination in the thalamus is blocked by application of TTX to the eyes. This finding is distinct from the findings of previous experiments because TTX specifically blocks only presynaptic activity, not pre- and postsynaptic activity. Previous experiments from the same group showed that specifically blocking postsynaptic NMDA receptors with APV also prevented the formation of ON/OFF sublamination in the thalamus, but not of eye-specific laminae. This means that blocking either presynaptic action potentials or postsynaptic responses prevents the formation of ON/OFF sublaminae. Yet, it appears that postsynaptic activity through the NMDA receptor is not necessary for the formation of eye-specific laminae.
13. Wong RO, Oakley DM: **Changing patterns of spontaneous bursting activity of on and off retinal ganglion cells during development.** *Neuron* 1996, **16**:1087-1095.
 14. Fischer KF, Lukasiewicz PD, Wong RO: **Age-dependent and cell class-specific modulation of retinal ganglion cell bursting activity by GABA.** *J Neurosci* 1998, **18**:3767-3778.
- This paper extends previous work by showing that the development-related changes in spontaneous activity of ON and OFF ferret retinal ganglion cells

are attributable to GABAergic influences: before the changes in ON/OFF spontaneous activity, GABA is excitatory, whereas after the developmental changes in spontaneous activity, GABA is inhibitory, but much more so for ON than OFF cells. This presumably causes the ON cells to burst less frequently than the OFF cells.

15. Miller KD: **Synaptic economics: competition and cooperation in synaptic plasticity.** *Neuron* 1996, **17**:371-374.

16. Angelucci A, Clasca F, Bricolo E, Cramer KS, Sur M: **Experimentally induced retinal projections to the ferret auditory thalamus: development of clustered eye-specific patterns in a novel target.** *J Neurosci* 1997, **17**:2040-2055.

Deafferentation of auditory thalamus causes some retinal axons to form permanent connections in the auditory thalamus. There is no need to ablate the LGN or VC, just 'free up' the auditory thalamus (MGN). When this happens, the retinal axons from the two eyes form permanent connections in the MGN that tend to be eye specific. There are no 'eye lamina', but local clusters of retino-MGN axons tend to be from the same eye.

17. Hubel DH, Wiesel TN: **Early exploration of the visual cortex.** *Neuron* 1998, **20**:401-412.

A fascinating historical perspective of the original experiments describing visual cortical receptive fields and the effects of form deprivation on visual cortical responses.

18. Horton JC, Hocking DR: **An adult-like pattern of ocular dominance columns in striate cortex of newborn monkeys prior to visual experience.** *J Neurosci* 1996, **16**:1791-1807.

19. Crair MC, Gillespie DC, Stryker MP: **The role of visual experience in the development of columns in cat visual cortex.** *Science* 1998, **279**:566-570.

The authors show that visual experience does not determine the pattern of cortical (orientation) maps. However, they report that spontaneously generated activity that is intrinsic to the neural circuits could help establish the pattern of orientation domains. This spontaneous activity would need to have special statistical properties to account for the observed 'matching' of orientation maps between the eyes, even in the absence of visual experience. Visual experience does appear to be necessary for the long-term maintenance of responsivity and selectivity. The authors also report that ocular dominance columns develop significantly earlier (by at least one week) than previously reported. This suggests that there may be two distinct stages during ocular dominance column development: map development, followed by map plasticity.

20. Erwin E, Miller KD: **Correlation-based development of ocularly matched orientation and ocular dominance maps: determination of required input activities.** *J Neurosci* 1998, **18**:9870-9895.

21. Wiesel TN, Hubel DH: **Single-cell responses in striate cortex of kittens deprived of vision in one eye.** *J Neurophysiol* 1963, **26**:1003-1017.

22. Horton JC, Hocking DR: **Timing of the critical period for plasticity of ocular dominance columns in macaque striate cortex.** *J Neurosci* 1997, **17**:3684-3709.

Elegantly delineates the critical period for the effects of monocular deprivation on the development of ocular dominance columns in monkeys. Shows that the effects of deprivation gradually decrease with age, the earliest deprivations being the most severe. The effect of deprivations at a few weeks after birth are less severe than those that started just after birth.

23. Crair MC, Ruthazer ES, Gillespie DC, Stryker MP: **Relationship between the ocular dominance and orientation maps in visual cortex of monocularly deprived cats.** *Neuron* 1997, **19**:307-318.

This paper describes the effect of monocular visual deprivation on the development of orientation and ocular dominance maps in the visual cortex of the cat. Monocular deprivation causes response to the deprived eye to cluster in patches located near the orientation singularities ('pinwheels') of the orientation map. These patches of deprived eye responsive cells are also poorly selective for stimulus orientation.

24. 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.

25. Shatz CJ, Lindstrom S, Wiesel TN: **The distribution of afferents representing the right and the left eyes in the cat's visual cortex.** *Brain Res* 1977, **131**:103-116.

26. Lowel S: **Ocular dominance column development: strabismus changes the spacing of adjacent columns in cat visual cortex.** *J Neurosci* 1994, **14**:7451-7468.

27. Lowel S, Singer W: **Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity.** *Science* 1992, **255**:209-212.

28. Schmidt KE, Kim DS, Singer W, Bonhoeffer T, Lowel S: **Functional specificity of long-range intrinsic and interhemispheric connections in the visual cortex of strabismic cats.** *J Neurosci* 1997, **17**:5480-5492.

This paper describes an extension of a previous study [52] concerning the effects of strabismus on the development of orientation and ocular dominance maps in the cat. In normal cats, callosal connections link like orientation domains. In strabismic cats, callosal connections link like orientation and like ocular dominance domains. This is the same effect as has been noted for cortico-cortical connections in strabismic cats.

29. Ruthazer ES, Stryker MP: **The role of activity in the development of long-range horizontal connections in area 17 of the ferret.** *J Neurosci* 1996, **16**:7253-7269.

30. Reh TA, Constantine-Paton M: **Eye-specific segregation requires neural activity in three-eyed *Rana pipiens*.** *J Neurosci* 1985, **15**:1132-1143.

31. Constantine-Paton M, Cline HT, Debski I: **Patterned activity, synaptic convergence, and the NMDA receptor in developing visual pathways.** *Annu Rev Neurosci* 1990, **13**:129-154.

32. Brickley SG, Dawes EA, Keating MJ, Grant S: **Synchronizing retinal activity in both eyes disrupts binocular map development in the optic tectum.** *J Neurosci* 1998, **18**:1491-1504.

Continuous strobe rearing partially disrupts the development of tectal maps and causes somewhat enlarged retino-tectal receptive fields, partially mismatched isthmo-tectal ipsilateral receptive fields, and interferes with the remapping that usually takes place after eye rotation. These findings suggest that activity is not just permissive, but also instructive.

33. Catalano SM, Chang CK, Shatz CJ: **Activity-dependent regulation of NMDAR1 immunoreactivity in the developing visual cortex.** *J Neurosci* 1997, **17**:8376-8390.

The level of NMDAR1 subunit expression correlates with the critical period for plasticity in developing cat visual cortex, and is modulated by visual experience. These experiments, though correlative, suggest that neuronal activity mediated by the NMDA receptor may help define plasticity windows during development.

34. Trepel C, Duffy KR, Pegado VD, Murphy KM: **Patchy distribution of NMDAR1 subunit immunoreactivity in developing visual cortex.** *J Neurosci* 1998, **18**:3404-3415.

NMDAR1 subunit expression is patchy in developing cortex, with some association to the borders of ocular dominance columns. The patchy pattern is prevented with monocular deprivation.

35. Cline HT, Debski I, Constantine-Paton M: **NMDA receptor antagonist desegregates eye specific stripes.** *Proc Natl Acad Sci USA* 1987, **84**:4342-4345.

36. Hickmott PW, Constantine-Paton M: **Experimental down-regulation of the NMDA channel associated with synapse pruning.** *J Neurophysiol* 1997, **78**:1096-1107.

37. Crair MC, Malenka RC: **A critical period for long-term potentiation at thalamocortical synapses.** *Nature* 1995, **375**:325-328.

38. Hestrin S: **Developmental regulation of NMDA receptor-mediated synaptic currents at a central synapse.** *Nature* 1992, **357**:686-689.

39. Carmignoto G, Vicini S: **Activity-dependent decrease in NMDA receptor responses during development of the visual cortex.** *Science* 1992, **258**:1007-1011.

40. Flint AC, Maisch US, Weishaupt JH, Kriegstein AR, Monyer H: **NR2A subunit expression shortens NMDA receptor synaptic currents in developing neocortex.** *J Neurosci* 1997, **17**:2469-2476.

The subunit composition of the NMDA receptor determines the kinetics of the current response. Neocortical cells expressing the NMDA NR2A subunit have faster and smaller currents than those expressing the NR2B subunit. The proportion of cells in cortex expressing the NR2A subunit increases developmentally, leading most cells to have faster and smaller NMDA currents in adults. This suggests that regulation of the NMDA receptor might also help regulate cortical plasticity.

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

42. Miller KD, Chapman, B, Stryker MP: **Visual responses in adult cat visual cortex depend on N-methyl-D-aspartate receptors.** *Proc Natl Acad Sci USA* 1989, **86**:5183-5187.

43. Roberts EB, Meredith MA, Ramoa AS: **Suppression of NMDA receptor function using antisense DNA blocks ocular dominance plasticity while preserving visual responses.** *J Neurophysiol* 1998, **80**:1021-1032.

The reduction of NMDA currents following antisense oligonucleotide blockade of NMDA receptor expression blocks ocular dominance plasticity with-

out blocking visual cortical responses. This finding implies that the pattern of activity (which involves Ca^{2+} influx) is critical for developmental plasticity. This activity is not just permissive, because visual cortical response appears 'normal' even though plasticity is impaired.

44. Tessier-Lavigne M, Goodman CS: **The molecular biology of axon guidance.** *Science* 1996, **274**:1123-1133.

45. Catalano SM, Shatz CJ: **Activity-dependent cortical target selection by thalamic axons.** *Science* 1998, **281**:559-562.

Shows that even very early stages in thalamocortical development, such as axon pathfinding, may be activity dependent. This finding is entirely consistent with a permissive role for activity, but the results are surprising because they show that even the selection of appropriate cortical targets, in this case visual cortex versus auditory cortex, may rely on an activity-dependent mechanism. Previously, these early stages of axon pathfinding were thought to be activity independent.

46. Dantzker JL, Callaway EM: **The development of local, layer-specific visual cortical axons in the absence of extrinsic influences and intrinsic activity.** *J Neurosci* 1998, **18**:4145-4154.

Spontaneous activity helps pattern intracortical connections, specifically layer 6 to layer 4 neurons. The experiments were performed on organotypic slice cultures from young ferret primary visual cortex, taken before they have formed substantial intracortical connections. The authors studied the pattern of local axonal connections of layer 6 neurons (axon collaterals) to layer 4 after culturing these cortical slices *in vitro*. In the presence of TTX (and therefore in the absence of spontaneous activity), layer 6 neurons are equally likely to arborize in layer 5 or layer 4. *In vivo*, or in slices cultured without TTX, layer 6 neurons preferentially arborize in layer 4. These findings suggest that the correct patterning of intracortical connections, at least of layer 6 pyramidal cells, requires spontaneous neural activity, but does not rely on sensory experience. No attempt was made to alter the pattern of spontaneous activity, so no conclusions can be drawn about the instructive versus permissive role of neural activity in this model.

47. Chiaia NL, Fish SE, Bauer WR, Bennett-Clarke CA, Rhoades RW: **Postnatal blockade of cortical activity by tetrodotoxin does not disrupt the formation of vibrissa-related patterns in the rat's somatosensory cortex.** *Brain Res Dev Brain Res* 1992, **66**:244-250.

48. Schlaggar BL, Fox K, O'Leary DDM: **Postsynaptic control of plasticity in developing somatosensory cortex.** *Nature* 1993, **364**:623-626.

49. Fox K, Schlaggar BL, Glazewski S, O'Leary DDM: **Glutamate receptor blockade at cortical synapses disrupts development of thalamocortical and columnar organization in somatosensory cortex.** *Proc Natl Acad Sci USA* 1996, **93**:5584-5589.

50. 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.

51. Iwasato T, Erzurumlu RS, Huerta PT, Chen DF, Sasaoka T, Ulupinar E, Tonegawa S: **NMDA receptor-dependent refinement of somatotopic maps.** *Neuron* 1997, **19**:1201-1210.

Reports the results of NMDAR1 knockout mice that have been 'rescued' by the ectopic expression of an NMDAR1 transgene. Mice that have a low level of expression of this transgene are similar to total knockouts, without barrels, but live longer (about 3 weeks). Mice that have a high expression level of the NMDAR1 transgene live to adulthood and have normal barrels. This strongly suggests that activity acting through the NMDA receptor is at least permissive for the development of the full 'barrel-type' somatotopic map.

52. Lowel S, Singer W: **Selection of intrinsic horizontal connection in the visual cortex by correlated neuronal activity.** *Science* 1992, **255**:209-212.

