nature neuroscience

© 2007 Nature Publishing Group http://www.nature.com/natureneuroscience

# Experience-dependent binocular competition in the visual cortex begins at eye opening

Spencer L Smith & Joshua T Trachtenberg

**Visual experience begins at eye opening, but current models consider cortical circuitry to be resistant to experience-dependent competitive modification until the activation of a later critical period. Here we examine this idea using optical imaging to map the time course of receptive field refinement in normal mice, mice in which the contralateral eye never opens and mice in which the contralateral eye is silenced. We found that the refinement of ipsilateral eye retinotopy is retarded by contralateral deprivation, but accelerated by silencing of the contralateral eye. Patterned visual experience through the ipsilateral eye is required for this acceleration. These differences are most obvious at postnatal day 15, long before the start of the critical period, indicating that experience-dependent binocular plasticity occurs much earlier than was previously thought. Furthermore, these results suggest that the quality of activity, in terms of signal to noise, and not the quantity, determines robust receptive field development.**

Experience-dependent competitive interactions between the inputs from the two eyes sculpt and ultimately consolidate cortical circuitry to its adult form. This plasticity, traditionally detected from changes in the ratio of cortical responses evoked by stimulation to each eye, is believed to be restricted to a well-defined critical period[1,2]. In mice, cats and ferrets, the critical period begins 7–10 d after eye opening[1–4] but can be accelerated or delayed by manipulating cortical inhibition[5–7]. During the precritical period, the time between eye opening and the activation of the critical period, many aspects of mature visual cortical circuitry develop independent of visual experience. For example, orientation tuning[8–11], the clustering of horizontal connections in supragranular layers[12] and the peak-to-peak periodicity of each eye's thalamocortical projections[13,14] mature to near adult levels in the absence of vision. However, patterned vision is required for the maintenance of adult-like receptive fields, and the age at which this requirement begins coincides with the onset of the critical period for cortical plasticity[8]. Thus, the progressive functional maturation of cortical circuitry is thought to involve two stages: (i) the establishment and refinement of receptive fields during the precritical period by intrinsic mechanisms, and (ii) the strengthening and consolidation of receptive field architecture during the critical period by competitive mechanisms that require visual experience (**Fig. 1a**). In this study, we reexamine this model in light of recent evidence that early visual experience influences the formation[15] and strength[16,17] of cortical synapses, the expression of immediate early genes[18] and the emergence of direction selectivity[19]. Using intrinsic signal optical imaging, we test the function of experience-dependent binocular competition in the establishment and subsequent maturation of each eye's retinotopic map during the precritical period in the mouse visual cortex (**Fig. 1b**). We show that maps of contralateral and ipsilateral eye retinotopy rapidly mature over the 10 d after eye opening, and that this maturation requires visual experience. Contrary to conventional views, we find that the rate of ipsilateral eye maturation is sensitive to the pattern of activity through the contralateral eye. Unpatterned visual experience through a deprived contralateral eye strongly retards the refinement of ipsilateral eye retinotopic maps, whereas removing or silencing the contralateral eye accelerates this maturation. The susceptibility of ipsilateral eye maps to activity through the contralateral eye demonstrates that experience-dependent binocular competition regulates the maturation of cortical circuitry from the moment the eyes open, long before the onset of the classically defined critical period. Notably, the accelerated maturation of ipsilateral eye maps in the absence of contralateral eye activity is not seen if the ipsilateral eye is itself deprived of patterned vision.

## RESULTS

### Normal maturation of cortical maps

To measure the time course for the normal maturation of cortical retinotopy to stimuli presented through the ipsilateral and contralateral eyes, we acquired movies of intrinsic optical signals as the mice viewed a bar of light moving at a fixed frequency. Fourier analysis of each pixel location's change in reflectivity generated two maps: a magnitude map of response amplitude at stimulus frequency and a phase map representing the time of the cortical response in the stimulus cycle[20] (**Fig. 2a**). Thus, the phase map is a retinotopic map of isoelevation in the visual field. Maps were generated for mice from P13, 1–3 d after natural eye opening, to P23, the beginning of the critical period for experience-dependent plasticity[2,21]. To evaluate the organization of the phase maps, we measured 'map scatter', the average difference in phase between each pixel in the map and the 24 surrounding pixels. In this metric, measured

Department of Neurobiology, University of California at Los Angeles, 695 Charles Young Drive South, Los Angeles, California, 90095-1761, USA. Correspondence should be addressed to J.T.T. (jtrachtenberg@mednet.ucla.edu).

Received 19 September 2006; accepted 5 January 2007; published online 11 February 2007; doi:10.1038/nn1844

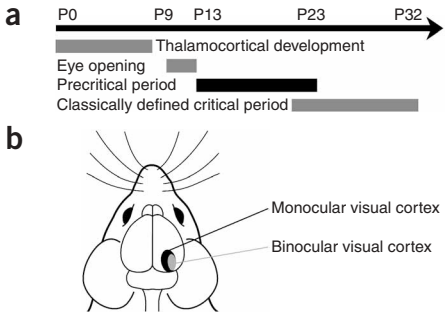


**Figure 1** Visual system of the mouse. (**a**) Time course of visual system development in the mouse. Eye opening occurs around P10–P13, and the classically defined critical period begins around P21–P23. (**b**) A schematic of the mouse visual pathway. Binocular visual cortex occupies the lateral third of the visual cortex. In adult mice, most cells in the binocular cortex receive input from both eyes.

in degrees, less scatter is indicative of a smoother map and greater precision in receptive field organization[22]. Cortical responsiveness was measured as the maximum pixel value in the magnitude maps.

In normal mice at P13, cortical responsiveness to visual stimulation was weak for both eyes, but contralateral eye retinotopic maps already showed greater organization than ipsilateral eye retinotopic maps ($P = 0.016$; **Fig. 2b**). By P15 contralateral eye maps of magnitude and retinotopy improved significantly relative to their values at P13 (magnitude, $P = 0.0046$; scatter, $P = 0.040$; **Fig. 2c**). In contrast, ipsilateral eye maps were only marginally stronger at P15 than P13 ($P = 0.040$), though retinotopic maps remained poorly organized ($P = 0.053$). A between-eye comparison confirmed that at P15 contralateral eye maps were stronger ($P = 0.037$) and better organized ($P = 0.00064$) than ipsilateral eye maps. By P17, ipsilateral eye maps improved significantly relative to their P15 values (magnitude, $P = 0.023$; scatter, $P = 0.0028$) and were then equivalent to contralateral eye maps (magnitude, $P = 0.38$; scatter, $P = 0.32$; **Fig. 2b,c**). Thus, ipsilateral eye maps develop more slowly than contralateral eye maps until P17. Thereafter, we found no further improvement in organization or peak responsiveness of ipsilateral eye or contralateral eye maps ($P > 0.14$, P17 versus P19–23 pooled).

## Contralateral deprivation retards map refinement

To explore whether patterned vision and binocular interactions regulate the refinement of each eye's cortical representation, we induced a mismatch in the pattern of activity through the two eyes by preventing the contralateral eye from ever opening naturally. Mice were monocularly deprived at P9, which is 1–3 d before eye opening. Therefore, the contralateral eye never experienced normal vision, whereas the ipsilateral eye opened naturally sometime between P10 and P12. At P13, contralateral eye maps of retinotopy and responsiveness from mice deprived of vision through this eye were indistinguishable from those of nondeprived mice (compare **Figs. 1** and **2**; for scatter, $P = 0.43$; for magnitude, $P = 0.96$). Notably, the scatter values for the contralateral and ipsilateral eye retinotopic maps were indistinguishable in contralaterally deprived P13 mice. This is quite different from what was seen in normal mice, where scatter values are significantly lower for contralateral eye maps compared to ipsilateral eye maps ($P = 0.016$; **Fig. 1b**). This result suggests that the 1–3 d of visual experience between eye opening and P13 in normal mice is probably responsible for the better retinotopic organization of contralateral eye maps relative to ipsilateral eye maps observed at P13.

By P15, retinotopic maps for the contralateral eye were significantly less organized ($P = 0.00045$; **Fig. 3a**) and response amplitudes were diminished in the contralaterally deprived mice relative to age-matched controls ($P = 0.011$; **Fig. 3b**). Maps of contralateral eye retinotopy from these mice slowly improved, despite continued deprivation, but remained significantly worse than those of nondeprived animals (P19–P23, $P = 0.0084$; **Fig. 3a**). The deficit in contralateral eye map responsiveness was also persistent (P19–P23, $P = 0.000020$; **Fig. 3b**). Notably, contralateral deprivation also significantly impeded the development of ipsilateral eye cortical maps, even though vision was normal through the ipsilateral eye (**Fig. 3**). From P17 to P23, maps of

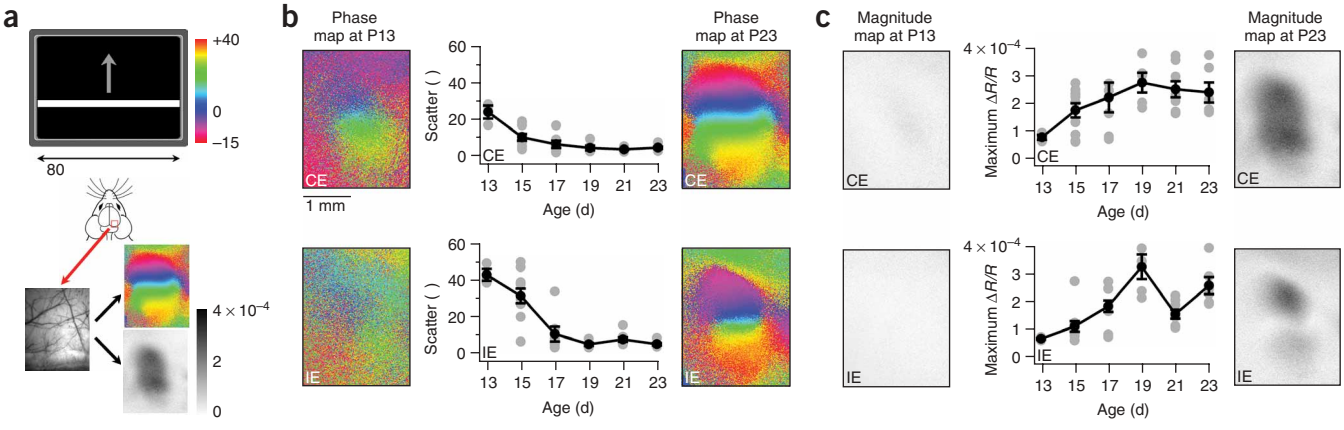


**Figure 2** Time course of normal development of retinotopic maps in mouse visual cortex. (**a**) Illustration of the visual stimulus used to map retinotopy. The color scale indicates the position of the stimulus bar on the monitor and the cortical region responding to this receptive field in the phase maps of isoelevation retinotopy. For each mouse, images of cortical vasculature, phase and magnitude were obtained. The scale bar shows the response magnitude as fractional change in reflectance over baseline reflectance ($\Delta R/R$). (**b**) Time course of retinotopic map refinement for both eyes, flanked by example maps from a P13 and a P23 mouse for contralateral eye (top) and ipsilateral eye (bottom). Lower scatter values indicate smoother, more organized maps. (**c**) Maximum response is plotted as a function of age for both eyes. Flanking maps depict response strength from the same two mice as in **b**. In these and all subsequent plots, each lightly colored, filled circle represents a single animal. Dark circles represent the mean and error bars delineate the s.e.m.; $\Delta R/R$ is the change in reflectance over baseline reflectance.

© 2007 Nature Publishing Group http://www.nature.com/natureneuroscience

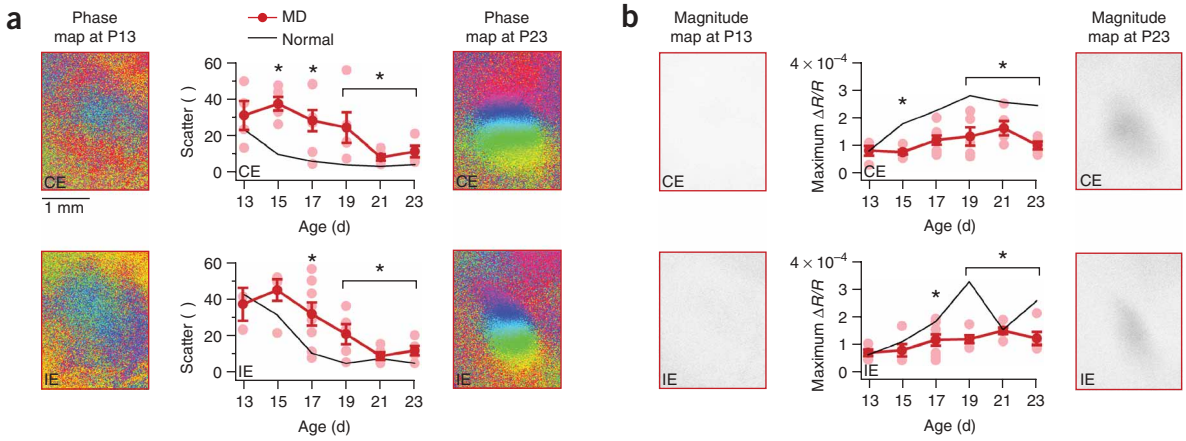


**Figure 3** Contralateral deprivation retards the maturation of ipsilateral eye maps. (**a**) Time course of retinotopic map refinement for both eyes in contralaterally deprived mice (monocular deprivation, MD), flanked by example maps from a P13 and a P23 mouse for deprived contralateral eye (top) and nondeprived ipsilateral eye (bottom). (**b**) Maximum response is plotted as a function of age for both eyes. Flanking maps depict response strength from the same two mice in **a**. Pink circles in all plots are values for individual animals. Black lines are data from normal animals shown in **Figure 2**. $^*P < 0.05$ compared to normal (two-tailed *t*-test). The scale bar shows the response magnitude as fractional change in reflectance over baseline reflectance ($\Delta R/R$).

ipsilateral eye retinotopy were significantly less organized and less responsive than in age-matched controls (scatter: P17, $P = 0.014$; P19–P23, $P = 0.0061$, **Fig. 3a**.; magnitude: P17, $P = 0.041$; P19–P23, $P = 0.00047$, **Fig. 3b**).

### Contralateral enucleation accelerates map refinement

To examine whether the effects of contralateral eye deprivation on ipsilateral eye maps are due to alterations in the pattern of activity through the contralateral eye or in the total activity through the contralateral eye, we enucleated the contralateral eye at P9, before eye opening but after the majority of retinogeniculate and thalamocortical projections have developed[22,23]. The organization of ipsilateral eye retinotopic maps in contralaterally enucleated mice was significantly improved at P15 relative to normal ($P = 0.0077$) or contralaterally deprived ($P = 0.015$) mice (**Fig. 4**). This accelerated maturation was not matched by an accelerated development of response magnitude (**Fig. 4b**). To confirm that the accelerated maturation of ipsilateral eye retinotopy resulted from an absence of contralateral eye activity rather than an injury artifact of enucleation, we performed a separate set of experiments in which we silenced contralateral eye activity from P9 to P15 with daily injections of 2-amino-4-phosphonobutyric acid (APB)[24]. As with contralateral enucleation, pharmacologically silencing the contralateral eye significantly accelerated the maturation of ipsilateral eye retinotopic maps relative to that of normal ($P = 0.0060$) or contralaterally deprived mice ($P = 0.0073$; **Fig. 4c,d**).

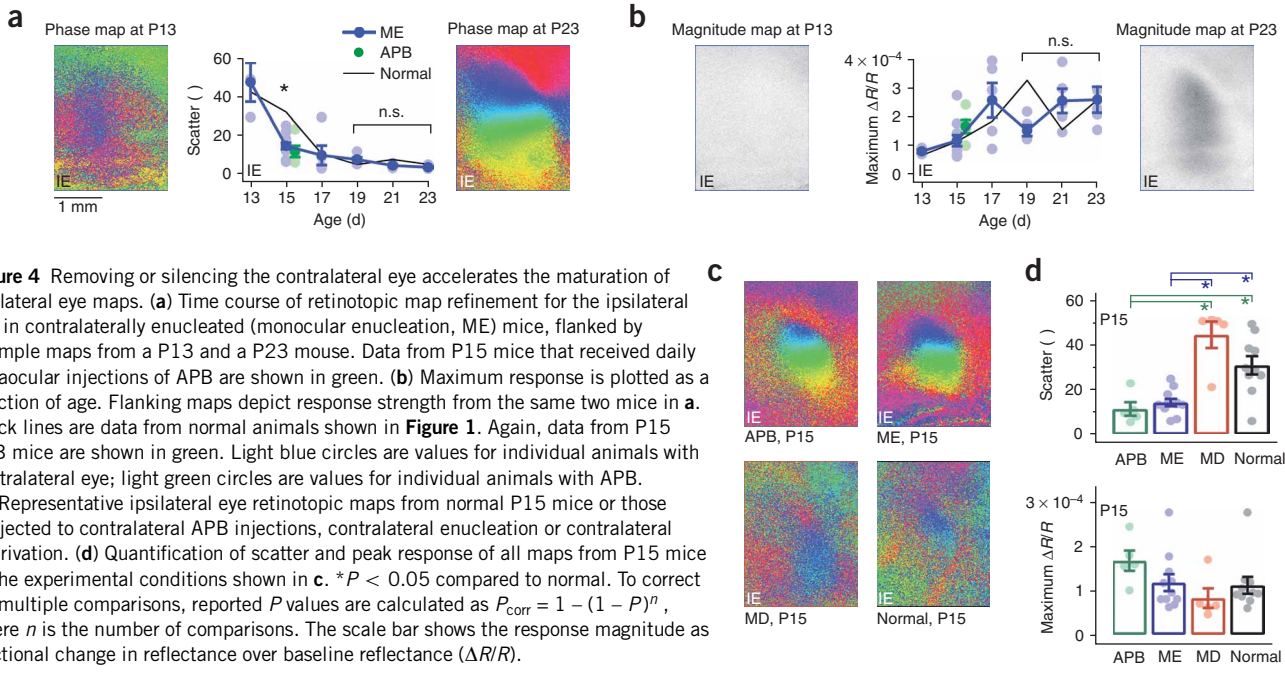


**Figure 4** Removing or silencing the contralateral eye accelerates the maturation of ipsilateral eye maps. (**a**) Time course of retinotopic map refinement for the ipsilateral eye in contralaterally enucleated (monocular enucleation, ME) mice, flanked by example maps from a P13 and a P23 mouse. Data from P15 mice that received daily intraocular injections of APB are shown in green. (**b**) Maximum response is plotted as a function of age. Flanking maps depict response strength from the same two mice in **a**. Black lines are data from normal animals shown in **Figure 1**. Again, data from P15 APB mice are shown in green. Light blue circles are values for individual animals with contralateral eye; light green circles are values for individual animals with APB. (**c**) Representative ipsilateral eye retinotopic maps from normal P15 mice or those subjected to contralateral APB injections, contralateral enucleation or contralateral deprivation. (**d**) Quantification of scatter and peak response of all maps from P15 mice in the experimental conditions shown in **c**. $^*P < 0.05$ compared to normal. To correct for multiple comparisons, reported *P* values are calculated as $P_{corr} = 1 - (1 - P)^n$, where *n* is the number of comparisons. The scale bar shows the response magnitude as fractional change in reflectance over baseline reflectance ($\Delta R/R$).

© 2007 Nature Publishing Group http://www.nature.com/natureneuroscience

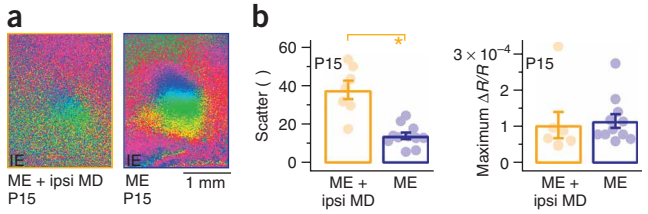


**Figure 5** Patterned visual experience is required for retinotopic map development. (**a**) Example retinotopic maps from mice in which the contralateral eye was enucleated (ME data are from **Fig. 3**) or, in addition, the ipsilateral eye was deprived. (**b**) Quantification of scatter and peak response of all maps from P15 mice in both conditions shown in **a**. $^*P < 0.05$ compared to normal. The scale bar shows the response magnitude as fractional change in reflectance over baseline reflectance ($\Delta R/R$).

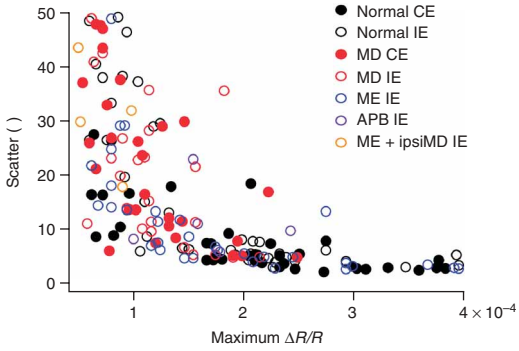


**Figure 6** Well-organized, low-scatter retinotopic maps can be detected even when the maximum response magnitude is low. The map scatter values for all mice are plotted versus the maximum response magnitudes for the associated magnitude maps. The density of points in the lower left corner demonstrates that the imaging paradigm employed can detect well-organized, low-scatter maps even when the maximum response magnitude is weak.

### Patterned vision is required for normal map refinement

In contralaterally enucleated mice, ipsilateral eye retinotopic maps were as poorly organized at P13 as in control animals, despite 4 d of activity in the absence of any competition from the contralateral eye. This suggested to us that the pattern of visual experience, rather than an absolute difference in activity between the two eyes[25], drives competitive plasticity at these young ages. To examine this, we enucleated the contralateral eye at P9 and prevented the ipsilateral eye from opening naturally until P15, when ipsilateral eye retinotopy is well organized in contralaterally enucleated mice (**Fig. 4a**). In these animals, the deprived ipsilateral eye is the only input to area V1. Maps of ipsilateral eye retinotopy were significantly less organized in these mice than in contralaterally enucleated mice with normal ipsilateral eye vision ($P = 0.0033$; **Fig. 5a**,**b**). However, the magnitudes of intrinsic optical signal responses in these two groups were not significantly different ($P = 0.95$; **Fig. 5c**), further supporting a dissociation between cortical activity and retinotopic map maturation. These observations support an instructive function for patterned vision in the maturation of ipsilateral eye retinotopic maps.

## DISCUSSION

The data we present here support three main conclusions. First, experience-dependent binocular competition drives map refinement from eye opening. Decorrelating the spatiotemporal patterns of contralateral and ipsilateral eye activity by contralateral eye lid suture retarded the refinement of ipsilateral eye maps even though the ipsilateral eye experienced normal vision (**Fig. 3**). Removing contralateral eye activity by enucleation accelerated ipsilateral eye map refinement (**Fig. 4**). These observations challenge the conventionally held view that experience-dependent plasticity begins in the fourth postnatal week[1,4]. This view is derived largely from single-unit electrophysiology recordings of ocular dominance, which measure the relative responsiveness of each recorded cell to stimulation through each eye. We show that contralateral eye deprivation prevents the strengthening of cortical responses to visual stimulation not only through the contralateral eye, but through the open ipsilateral eye as well. Therefore, a ratiometric analysis of ocular dominance may miss the competitive plasticity we report here.

Second, binocular competition during the precritical period is not mediated by the relative strength of each eye's input. Contralateral eye deprivation degrades cortical responsiveness to this eye, and yet the ipsilateral eye is less capable of refining its cortical representation, despite facing a weaker competitor (**Fig. 3**). Furthermore, depriving the ipsilateral eye of patterned vision impedes map refinement, even in the absence of any activity from the contralateral eye, as in the case of contralateral eye enucleation (**Fig. 5**). Instead of purely activity-based competition, our data support a model of correlation-based Hebbian plasticity, in which inputs from the two eyes compete temporally to regulate the firing of binocular cortical neurons[26]. In this model, ipsilateral eye inputs rapidly strengthen where they are coactive with contralateral eye inputs, or in enucleated animals lacking contralateral eye inputs. In binocular zones, this model predicts that rapidly maturing contralateral eye inputs serve as a template for ipsilateral eye maturation, aligning the two eyes' maps. In circumstances where the activity of the two eyes is of equal strength but uncorrelated, there is no clear 'teacher' or 'student'. In the case of contralateral lid suture, unpatterned activity through the deprived contralateral eye impedes the refinement of contralateral eye maps but also decorrelates contralateral and ipsilateral eye activities. This forces the ipsilateral eye inputs to drive cortical spiking on their own, without the aid of a 'teacher'. Although immature ipsilateral eye inputs can drive cortical responses by themselves, as evidenced by their rapid refinement following contralateral enucleation, the 'noise' source from the deprived contralateral eye degrades the temporal correlation between ipsilateral eye afferent activity and cortical spiking, thus slowing the refinement of ipsilateral eye retinotopic maps. Notably, the plasticity we report here precedes the maturation of cortical inhibitory circuitry[5,6,27]. Correlation-based plasticity[28] does not require inhibition[26,29], though inhibition would be expected to augment this plasticity mechanism by enabling well-timed responses.

Third, the quality of sensory experience profoundly affects the refinement of cortical receptive fields. Degrading patterned vision in either eye by lid suture prevented the normal maturation of that eye's cortical maps of retinotopy and responsiveness (**Figs. 3** and **5**). Similar findings have been reported with binocular manipulations in ferrets[9]. Dark rearing, which deprives the cortex of all visually driven activity, mildly impedes the normal maturation of orientation tuning in this system. In contrast, binocular deprivation, which alters the temporal and spatial characteristics of visual experience, prevents the maturation of orientation tuning. Our results support the conclusion that the quality, rather than the quantity, of sensory experience determines cortical maturation.

Our results extend prior studies of the detrimental impact of noise on cortical circuit refinement[30–32] to include noise competing with patterned inputs. We provide the first evidence that poorly patterned activity through the deprived eye inhibits not only the refinement of the

© 2007 Nature Publishing Group http://www.nature.com/natureneuroscience

retinotopic map of the deprived eye[31], but also that of the nondeprived eye that is experiencing unimpeded vision. This speaks to a controversy regarding the treatment of anisometropic amblyopes. These individuals have eyes with mismatched resolving powers, resulting in neural circuitry that ignores visual information from one eye. Treatment of amblyopic infants typically involves occluding the dominant eye or blurring vision through this eye with atropine, with the goal of providing a competitive edge to the weaker eye and enabling it to increase its cortical territory. These approaches may retard the establishment of proper cortical circuitry for the weaker eye. Applying corrective optics may be a better therapeutic strategy[33,34].

## METHODS

**Optical imaging.** Mice (C57/Bl6, Taconic) were anesthetized with halothane (5% for induction, 1–2% for maintenance) and mounted in a stereotaxic frame. The eyes were covered with silicon oil. The scalp covering the right occipital cortex was resected and the skull covered with agar and a glass coverslip. The preparation was illuminated with 700-nm light and imaged with a tandem lens macroscope defocused 600 μm into the brain. Images were acquired with a 12-bit CCD camera (Dalsa 1M30), frame grabber (Matrox Meteor II/Dig) and custom software. The visual stimulus was a white horizontal bar, 1–2 degrees in height, which drifted up or down at 0.125 Hz on a black background. An 8-min-long movie was taken for each direction and each eye, for a total of four movies. Acquisition was at 30 frames per second, and the 12-bit frames were binned in software four times temporally and 2 × 2 spatially, resulting in 16-bit image files. From movies of these 16-bit files, Fourier analysis of each pixel column generated maps of magnitude and phase at 0.125 Hz[20]. Scatter was computed on phase maps that were corrected for hemodynamic delay using time reversal[20,22]. The region of interest was defined using the magnitude map after it had been smoothed using a 5 × 5 Gaussian filter. All pixels that had magnitude values ≥60% of the maximum magnitude value in the smoothed map were included in the scatter calculation. The phase value for each pixel in the masked phase map was compared to the average of its neighbors in a 5 × 5 box, and the average difference for each map was calculated. In practice, this method is capable of detecting retinotopic maps even when response magnitude is weak (**Fig. 6**). Maximum magnitude values were taken from unfiltered magnitude maps.

**Surgery.** All manipulations took place or were initiated at P9, which is 1–3 d before eye opening. Mice were lightly anesthetized with ketamine and xylazine or isoflurane. For monocular deprivation, the left eye was covered with a liquid bandage (NewSkin, Medtech) to prevent natural eye opening. For monocular enucleation, the conjectiva was trimmed, the eyeball displaced from the socket and the optic nerve tied off with 6-0 suture. The optic nerve was then cut and the eyeball was removed. Antibiotic ointment was placed in the orbit and the eyelid was sutured closed. Monocular enucleated mice received daily injections of carprofen analgesic for 2 d after surgery. All procedures involving the handling and use of mice for these experiments were approved by the University of California Los Angeles Office for Protection of Research Subjects and the Chancellor's Animal Research Committee.

**APB injections.** Mice were anesthetized with isoflurane. Intravitreal injections of APB were made posterior to the scleral margin using a 33-gauge Hamilton syringe to achieve a retinal concentration of 3.5 mM[24]. The efficacy of this concentration was verified by imaging cortical responses in P17 mice, then injecting APB. APB-injected mice showed an immediate loss of cortical responsiveness to visual stimulation.

**Statistics.** The two-tailed *t*-test and the Bonferroni correction for multiple comparisons (in **Fig. 4d**) were used to compute significance. All time points are represented by animals from at least two different litters. Paired *t*-tests were used when comparing ipsilateral eye maps to contralateral eye maps in control animals.

**ACKNOWLEDGMENTS**

We thank M. Stryker for suggesting the APB experiments and for helping to troubleshoot our imaging setup; E. Ruthazer for providing us with his enucleation protocol; and A. McGee, W. Thompson, J. Faguet, E. Ruthazer and M. Stryker for critically reading the manuscript. This work was supported by the US National Eye Institute, the Klingenstein Foundation and the Giannini Family Foundation.

**AUTHOR CONTRIBUTIONS**

S.L.S. conducted the experiments, wrote the computer code for image acquisition and analysis, conducted the data analyses and prepared the figures. J.T.T. conducted some of the experiments and supervised the project. S.L.S. and J.T.T. contributed equally to writing the manuscript.

**COMPETING INTERESTS STATEMENT**

The authors declare that they have no competing financial interests.

Published online at http://www.nature.com/natureneuroscience
Reprints and permissions information is available online at http://npg.nature.com/reprintsandpermissions

1. Hubel, D.H. & Wiesel, T.N. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J. Physiol. (Lond.)* **206**, 419–436 (1970).
2. Gordon, J.A. & Stryker, M.P. Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. *J. Neurosci.* **16**, 3274–3286 (1996).
3. Issa, N.P., Trachtenberg, J.T., Chapman, B., Zahs, K.R. & Stryker, M.P. The critical period for ocular dominance plasticity in the Ferret's visual cortex. *J. Neurosci.* **19**, 6965–6978 (1999).
4. Olson, C.R. & Freeman, R.D. Profile of the sensitive period for monocular deprivation in kittens. *Exp. Brain Res.* **39**, 17–21 (1980).
5. Huang, Z.J. *et al.* BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. *Cell* **98**, 739–755 (1999).
6. Fagiolini, M. & Hensch, T.K. Inhibitory threshold for critical-period activation in primary visual cortex. *Nature* **404**, 183–186 (2000).
7. Fagiolini, M. *et al.* Specific $GABA_A$ circuits for visual cortical plasticity. *Science* **303**, 1681–1683 (2004).
8. Crair, M.C., Gillespie, D.C. & Stryker, M.P. The role of visual experience in the development of columns in cat visual cortex. *Science* **279**, 566–570 (1998).
9. White, L.E., Coppola, D.M. & Fitzpatrick, D. The contribution of sensory experience to the maturation of orientation selectivity in ferret visual cortex. *Nature* **411**, 1049–1052 (2001).
10. Pettigrew, J.D. The effect of visual experience on the development of stimulus specificity by kitten cortical neurones. *J. Physiol. (Lond.)* **237**, 49–74 (1974).
11. Sherk, H. & Stryker, M.P. Quantitative study of cortical orientation selectivity in visually inexperienced kitten. *J. Neurophysiol.* **39**, 63–70 (1976).
12. Ruthazer, E.S. & Stryker, M.P. The role of activity in the development of long-range horizontal connections in area 17 of the ferret. *J. Neurosci.* **16**, 7253–7269 (1996).
13. Crowley, J.C. & Katz, L.C. Development of ocular dominance columns in the absence of retinal input. *Nat. Neurosci.* **2**, 1125–1130 (1999).
14. Crowley, J.C. & Katz, L.C. Early development of ocular dominance columns. *Science* **290**, 1321–1324 (2000).
15. Wallace, W. & Bear, M.F. A morphological correlate of synaptic scaling in visual cortex. *J. Neurosci.* **24**, 6928–6938 (2004).
16. Lu, W. & Constantine-Paton, M. Eye opening rapidly induces synaptic potentiation and refinement. *Neuron* **43**, 237–249 (2004).
17. Maffei, A., Nelson, S.B. & Turrigiano, G.G. Selective reconfiguration of layer 4 visual cortical circuitry by visual deprivation. *Nat. Neurosci.* **7**, 1353–1359 (2004).
18. Tagawa, Y., Kanold, P.O., Majdan, M. & Shatz, C.J. Multiple periods of functional ocular dominance plasticity in mouse visual cortex. *Nat. Neurosci.* **8**, 380–388 (2005).
19. Li, Y., Fitzpatrick, D. & White, L.E. The development of direction selectivity in ferret visual cortex requires early visual experience. *Nat. Neurosci.* **9**, 676–681 (2006).
20. Kalatsky, V.A. & Stryker, M.P. New paradigm for optical imaging: temporally encoded maps of intrinsic signal. *Neuron* **38**, 529–545 (2003).
21. Taha, S., Hanover, J.L., Silva, A.J. & Stryker, M.P. Autophosphorylation of alphaCaMKII is required for ocular dominance plasticity. *Neuron* **36**, 483–491 (2002).
22. Cang, J. *et al.* Development of precise maps in visual cortex requires patterned spontaneous activity in the retina. *Neuron* **48**, 797–809 (2005).
23. Godement, P., Salaun, J. & Imbert, M. Prenatal and postnatal development of retinogeniculate and retinocollicular projections in the mouse. *J. Comp. Neurol.* **230**, 552–575 (1984).
24. Chapman, B. Necessity for afferent activity to maintain eye-specific segregation in ferret lateral geniculate nucleus. *Science* **287**, 2479–2482 (2000).

© 2007 Nature Publishing Group http://www.nature.com/natureneuroscience

25. Chapman, B., Jacobson, M.D., Reiter, H.O. & Stryker, M.P. Ocular dominance shift in kitten visual cortex caused by imbalance in retinal electrical activity. *Nature* **324**, 154–156 (1986).
26. Song, S., Miller, K.D. & Abbott, L.F. Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. *Nat. Neurosci.* **3**, 919–926 (2000).
27. Hensch, T.K. Critical period plasticity in local cortical circuits. *Nat. Rev. Neurosci.* **6**, 877–888 (2005).
28. Miller, K.D., Keller, J.B. & Stryker, M.P. Ocular dominance column development: analysis and simulation. *Science* **245**, 605–615 (1989).
29. Feldman, D.E. Timing-based LTP and LTD at vertical inputs to layer II/III pyramidal cells in rat barrel cortex. *Neuron* **27**, 45–56 (2000).
30. Chang, E.F. & Merzenich, M.M. Environmental noise retards auditory cortical development. *Science* **300**, 498–502 (2003).
31. Weliky, M. & Katz, L.C. Disruption of orientation tuning in visual cortex by artificially correlated neuronal activity. *Nature* **386**, 680–685 (1997).
32. Zhou, Q., Tao, H.W. & Poo, M.M. Reversal and stabilization of synaptic modifications in a developing visual system. *Science* **300**, 1953–1957 (2003).
33. Vereecken, E.P. & Brabant, P. Prognosis for vision in amblyopia after the loss of the good eye. *Arch. Ophthalmol.* **102**, 220–224 (1984).
34. Isenberg, S.J. Amblyopia can be treated without occlusion or atropine. *Ophthalmology* **113**, 893 (2006).

© 2007 Nature Publishing Group http://www.nature.com/natureneuroscience