

Ipsilateral Eye Cortical Maps Are Uniquely Sensitive to Binocular Plasticity

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Faguet J, Maranhao B, Smith SL, Trachtenberg JT. Ipsilateral eye cortical maps are uniquely sensitive to binocular plasticity. *J Neurophysiol* 101: 855–861, 2009. First published December 3, 2008; doi:10.1152/jn.90893.2008. In the cerebral cortex, neuronal circuits are first laid down by intrinsic mechanisms and then refined by experience. In the canonical model, this refinement is driven by activity-dependent competition between inputs for some limited cortical resource. Here we examine this idea in the mouse visual cortex at the peak of the critical period for experience-dependent plasticity. By imaging intrinsic optical responses, we mapped the strength and size of each eye's cortical representation in normal mice, mice that had been deprived of patterned vision uni- or bilaterally, and in mice in which the contralateral eye had been removed. We find that for both eyes, a period of visual deprivation results in a loss of cortical responsiveness to stimulation through the deprived eye. In addition, the ipsilateral eye pathway is affected by the quality of vision through the opposite eye. Our findings indicate that although both contra- and ipsilateral eye pathways require visual experience for their maintenance, ipsilateral eye projections bear an additional, unique sensitivity to binocular interactions.

INTRODUCTION

Early life experience sculpts the structure and function of the cerebral cortex. The mechanisms driving this experience-dependent plasticity have been most extensively studied in the adolescent visual system where depriving one eye of vision results in cortical blindness to this eye even after vision is restored (Wiesel and Hubel 1963a,b, 1965). Concomitant with this loss is an increase in cortical responsiveness to the non-deprived eye.

The molecular underpinnings of cortical binocular plasticity have been intensively sought. Understanding these molecular mechanisms may illuminate novel avenues for the treatment of amblyopia. The molecules that regulate experience-dependent cortical plasticity may also play roles in the processes of learning and memory. For several reasons, the mouse has emerged as the preeminent model system for studying cortical binocular plasticity. In addition to the ease of genetic manipulation in mice, neurons in mouse visual cortex exhibit many of the same receptive field properties that have been characterized in carnivores and primates. As in these other species, the binocularity of neurons can be readily shifted by visual manipulation.

Recent work from our laboratory found that immediately after eye opening, ipsilateral eye cortical maps are strongly influenced by vision through the contralateral eye (Smith and Trachtenberg 2007). Work in cats indicates that ipsilateral eye maps require visual experience for their maturation, whereas contralateral eye maps do not (Crair et al. 1998). These

observations suggest that changes in cortical responsiveness following manipulations of ipsilateral eye vision are distinct from the changes induced by manipulations of contralateral eye vision. To characterize possible differences in the plasticity of contralateral and ipsilateral pathways, we measured the cortical response to various visual manipulations that began on postnatal day 28, the age of peak sensitivity to monocular deprivation. Mice were divided into six groups: controls with normal vision, binocular deprivation, contralateral deprivation, ipsilateral deprivation, contralateral enucleation, and contralateral enucleation with ipsilateral deprivation (Fig. 1).

We quantify changes in cortical function using intrinsic signal optical imaging. Intrinsic optical responses report metabolic changes driven by local neural activity (Grinvald et al. 1986), and their magnitude and spatial profile are well correlated with neuronal spiking (Masino 2003; Peterson et al. 1998) in all species and in all cortical areas where the technique has been applied. Importantly, intrinsic signal imaging is a reliable measure of visual cortical plasticity in mice. Changes in cortical responsiveness that have been measured with this technique have been verified with single unit electrophysiology (Hofer et al. 2006; Kaneko et al. 2008a,b).

We find that for the contralateral eye, the quality of its own vision is the sole determinant of its cortical representation. For the ipsilateral eye, its cortical representation is determined by the quality of its own vision as well as the quality of vision through the contralateral eye.

METHODS

Intrinsic signal optical imaging

Mice (C57BL/6, Charles River) were anesthetized with halothane (5% for induction, 2% thereafter) in pure oxygen and mounted in a stereotaxic frame. Halothane anesthesia reliably reports plastic changes in cortical responsiveness measured using intrinsic signal imaging (Hofer et al. 2006). The eyes were covered with silicon oil, the scalp was removed, and the soft tissue overlying the skull was resected. The skull was covered with 2% agarose and a glass coverslip. The right occipital cortex was illuminated with 700-nm light and imaged with a tandem lens microscope consisting of 35- and 135-mm focal length F-mount photographic lenses (Nikon), providing a $\times 3.9$ magnification. The microscope was defocused 600 μm beneath the cortical surface. For each stimulus, 8-min movies were acquired at 30 frames per second using a 12-bit CCD camera (Dalsa 1M30), a framegrabber (Matrox Meteor II/Dig) and custom software. Frames were binned four times temporally and 2×2 spatially.

For imaging the binocular zone, the visual stimulus was a horizontal white bar, 2.5° in height and 20° in width, spanning -15 to 5° in azimuthal space. The bar drifted up or down on a black background at 0.125 Hz. Up and down runs were acquired for each eye in the order:

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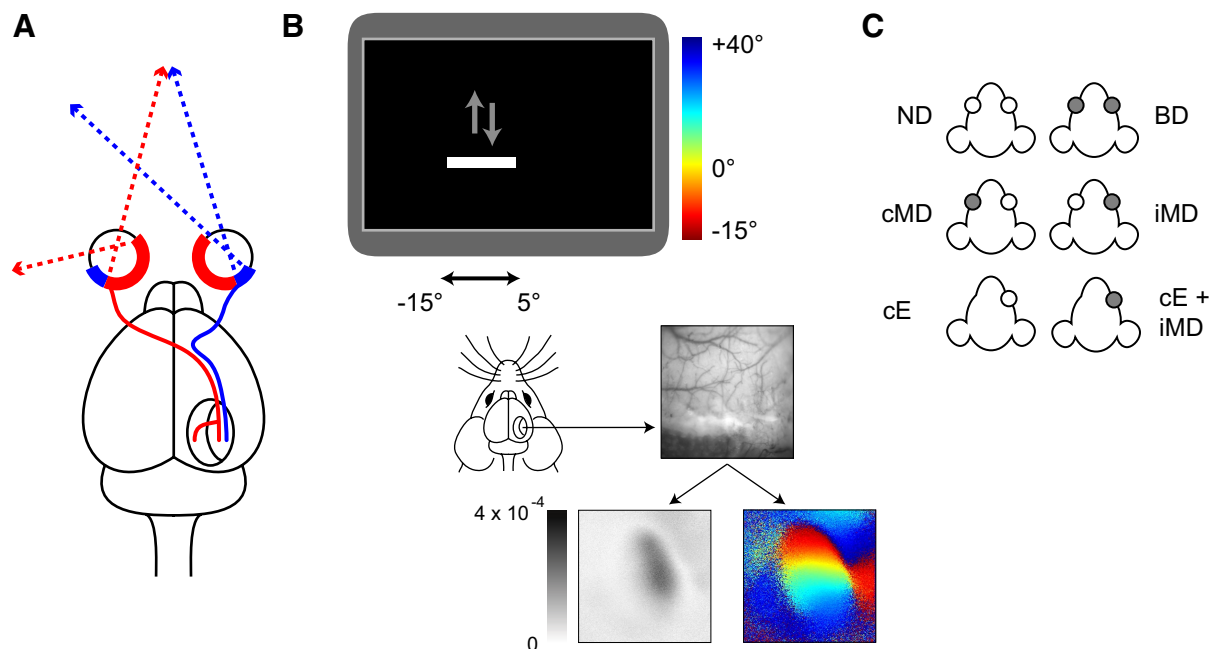


FIG. 1. Experimental overview. *A*: schematic of the mouse visual system. The medial, monocular portion of primary visual cortex receives input solely from the contralateral eye. The lateral, binocular zone receives input from both eyes and maps the central 30° of visual space. *B*: illustration of the stimulus used to map binocular visual cortex. Mice viewed a drifting bar of light subtending 20° in the center of their visual field. For each mouse, an image of cortical vasculature was acquired and then maps of magnitude and phase were generated. The magnitude map shows the strength and area of responsiveness. Its scale bar indicates change in reflectance over baseline reflectance ($\Delta R/R$). The phase map shows isoelevation retinotopy. The color scale next to the monitor and the coloration of the phase map indicate the vertical position of the stimulus, and the area of cortex responding to each position, respectively. *C*: summary of experimental manipulations. In all mice, the right hemisphere was imaged. Deprived eyes are 50% gray instead of black to emphasize residual light impinging on the retina (see Fig. 5). All manipulations began on postnatal day 28, the age of peak sensitivity to monocular deprivation. Mice were imaged following 2 wk of altered visual experience. ND, nondeprived; BD, binocular deprivation; cMD, contralateral monocular deprivation; iMD, ipsilateral monocular deprivation; cE, contralateral enucleation; cE+iMD, contralateral enucleation and ipsilateral monocular deprivation.

contralateral up, ipsilateral up, ipsilateral down, contralateral down. The order was kept constant between mice to control for gradually changing anesthesia. In mice where only one eye was imaged, blank runs were acquired. For monocular zone imaging, the stimulus was a similar horizontal bar spanning -105 to -30° in azimuth.

To examine the effects of deprivation on lower spatial frequencies and all orientations, we presented mice with a contrast-modulated stochastic noise stimulus. Visual stimuli were generated as described in published work from the Stryker laboratory (Gandhi et al. 2008; Neill and Stryker 2008). We slightly modified their approach as follows: the stochastic noise movie had a low-pass spatial cutoff of 0.04 cycle/°; it was contrast modulated with an 8 s period; it was generated at 100×100 pixels prior to interpolation. Note that all images acquired with this stimulus were done so using 1 mg/kg chlorprothixene with 0.5–0.75% isoflurane anesthesia and 610-nm light illumination. Imaging was conducted through cranial windows.

Image analysis

For each run, Fourier analysis produced a map of magnitude and phase at 0.125 Hz. Response strength was measured at 10% intervals below the peak pixel value in an eye's averaged up and down magnitude maps. All pixels in any given threshold were averaged. Thus in the plots of reflectance versus threshold (e.g., Fig. 2A), the change in reflectance at threshold 1 includes only the peak pixel value; the change in reflectance at 0.5 is the average of all pixels in the manually defined region of interest whose values are greater than half the peak pixel value. Area was measured as all the pixels included in the responsive area that were 2 SD above the mean background noise. Area measurements were converted into and expressed as square

millimeters. In phase maps (cf. Figs. 1 and 5), pixel values represent the time in the stimulus cycle when that region of cortex was responding. Thus phase maps are retinotopic maps of isoelevation in the visual field.

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. Lid sutures and enucleations began on postnatal day 28. In a few cases, manipulations began on P27 or P29, but in all cases, mice were imaged 2 wk later. For all recovery surgeries, mice were anesthetized with isoflurane (1–2%). Mice received daily injections of carprofen analgesia for 2 days after surgery.

For lid sutures, the eye(s) were covered with antibiotic ophthalmic ointment, and the lid margins were trimmed with iridectomy scissors. Two mattress sutures (6-0 silk) were placed through the eyelids. On the imaging day, sutured eyes were inspected under the dissecting microscope to ensure they remained completely closed. To control for possible damage done in opening sutured eyelids, the lids of all nondeprived eyes were also trimmed prior to imaging.

For enucleations, the connective tissue attached to the sclera was dissected using a No. 11 scalpel blade. The eye was then dislodged by pressing blunt forceps into the nasal corner of the socket. A loop of 6-0 silk suture was placed around the eye and tightened to ligate the optic nerve and ophthalmic artery. The eye was then cut from the nerve and artery and the suture trimmed short. After filling the orbit with antibiotic ointment, the lids were sutured together.

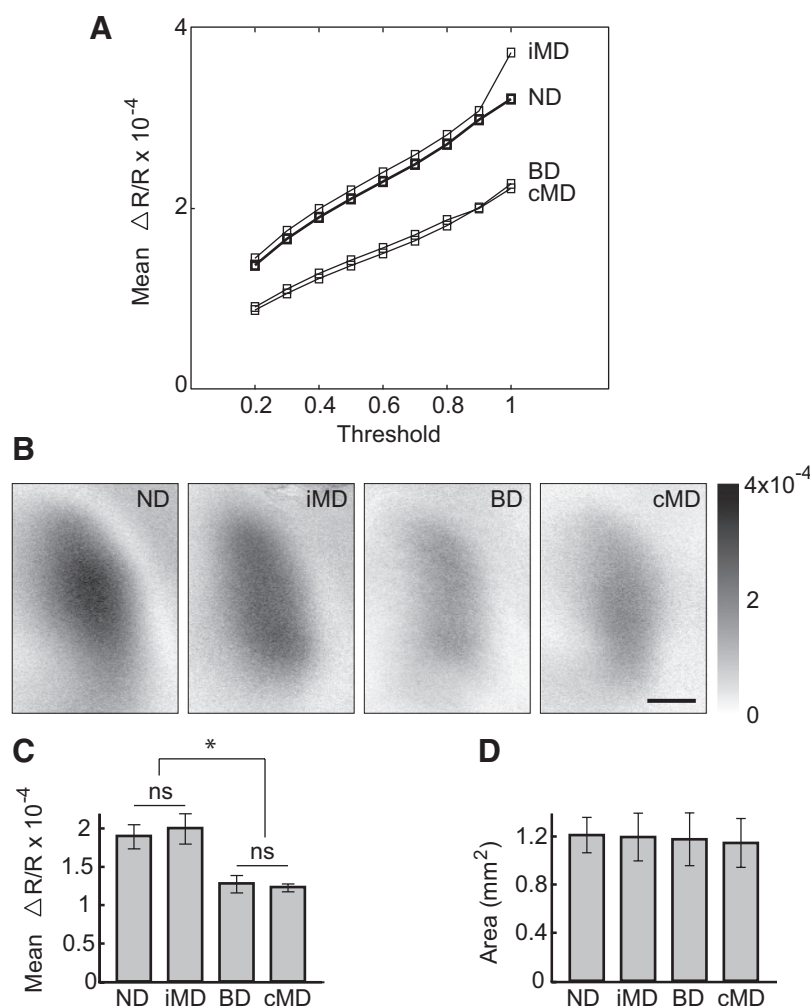


FIG. 2. Plasticity of the contralateral pathway in the binocular zone. **A:** strength of cortical response after each manipulation. The strength is measured as the average pixel value at each threshold. The strength at threshold 1 is the peak pixel value; the strength at threshold 0.5, for example, is the average strength of each pixel whose magnitude is $>50\%$ of the peak pixel value. Each line is the average across all mice in that group. The numbers of mice in each group are reported below, and in each figure legend hereafter. Error bars are omitted for clarity but are presented as SD at 0.4 threshold in **C**. **B:** example magnitude maps from contralateral eye visual stimulation in each paradigm. Abbreviations in the upper right of each image are as in Fig. 1. Scale bar is 500 μm . **C:** mean $\pm$ SD of the response magnitude for each condition measured at the 60% threshold (0.4 in **A**). *P* values for the appropriate comparisons are presented in the text. **D:** mean $\pm$ SD of the response area in square millimeters. *P* values for the appropriate comparisons are presented in the text. ND, *n* = 8; cMD, *n* = 8; BD, *n* = 9; iMD, *n* = 8.

Anterograde labeling of retinogeniculate projections

Cholera toxin B conjugated to Alexa Fluor 594 (CTB-Alexa Fluor 594) was used to label the size of the ipsilateral eye projection to the dorsal lateral geniculate nucleus of the thalamus (dLGN). P40 mice were anesthetized with 2% isoflurane and 0.5 μl 1% solution was injected into the right eye in mice with both eyes intact and in mice in which the left eye had been enucleated at P28. Animals were killed 3 days later and perfused transcardially with 0.9% saline followed by 4% paraformaldehyde in 0.1 M phosphate-buffered saline. Sections were cut at 100 μm thickness using a vibratome. All sections of the dLGN were digitally photographed at $\times 10$ magnification. The labeled area in each section was defined as pixels with 1.5 times the intensity value of the background. Background was defined for each image as the mean pixel value in a user-defined region of interest that contained no label. For each mouse, the total labeled volume was calculated by multiplying labeled areas by section thickness.

Statistics

Each experimental group consisted of animals from at least two litters. Significance was computed using two-tailed *t*-tests. All *t*-tests were unpaired except for the acute lid suture experiments in Fig. 5. Multiple comparisons were corrected for with the Holm-Bonferroni method.

RESULTS

Manipulations of visual experience began on postnatal day 28, the age of greatest cortical sensitivity to monocular deprivation (Gordon and Stryker 1996). Mice were imaged on postnatal day 42 after 2 wk of altered visual experience. Manipulations were prolonged so that our results would not be convolved with short-term and possibly transient changes in neuronal excitability that may occur after visual deprivation. Prolonged deprivations are also more relevant to human amblyopia.

Plasticity of contralateral eye maps

Monocular deprivation of the contralateral eye is the predominant model used to study binocular plasticity in the mouse (Frenkel and Bear 2004; Gordon and Stryker 1996). At postnatal day 28, 4 days of contralateral deprivation are sufficient to induce a robust shift in cortical ocular dominance (Gordon and Stryker 1996). In agreement with these earlier studies, we found that in the binocular zone, 2 wk of contralateral deprivation dramatically reduced the strength of cortical responsiveness to the deprived eye relative to nondeprived mice [Fig. 2C; *P* = 0.002 nondeprived (ND) vs. contralateral monocular deprivation (cMD)]. However, we observed no significant change in the area of responsive cortex (Fig. 2D; *P* = 0.95).

To examine whether the loss of contralateral cortical responsiveness was a result of visual deprivation per se or an

imbalance in the activity between the two eyes, we deprived another group of mice binocularly. Notably, contralateral eye maps were as severely weakened by prolonged binocular deprivation as when only the contralateral eye was shut [Fig. 2C; $P = 0.86$ binocular deprivation (BD) vs. cMD, $P = 0.001$ BD vs. ND]. Here again we found no difference from controls in the area of cortex responding to contralateral eye stimulation (Fig. 2D; $P = 0.99$ ND vs. BD). Nor was there a difference in area between binocularly deprived and contralaterally deprived mice (Fig. 2D; $P = 0.96$ BD vs. cMD).

We further investigated the roles of deprivation and binocular interactions by examining map plasticity in the monocular zone. This was done by restricting visual stimuli to the monocular visual space contralateral to the imaged hemisphere. As in binocular cortex, we found that two weeks of visual deprivation degraded cortical responsiveness (Fig. 3).

After observing similar effects of BD and cMD on contralateral eye maps, and the effect of deprivation on the monocular zone, we wondered whether contralateral eye maps are insensitive to ipsilateral eye activity. To examine this question from another angle, we left vision in the contralateral eye intact while altering vision in the ipsilateral eye with monocular deprivation. Two weeks of ipsilateral deprivation had no effect on contralateral eye maps relative to those in nondeprived mice (Fig. 2, C and D; $P = 0.99$ for responsiveness and area). Thus the primary and perhaps sole determinant of contralateral eye cortical responsiveness is the quality of vision through the contralateral eye. Binocular interactions do not appear to be influential.

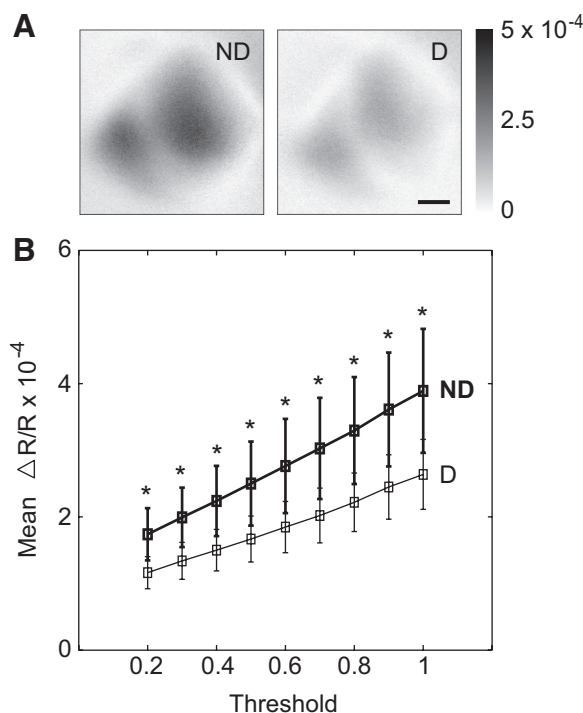


FIG. 3. Deprivation degrades the strength of monocular zone maps. A: example maps of the monocular zone from a nondeprived mouse (left) and a mouse that experienced 2 wk of vision through a sutured eyelid (right). Scale bar is 500 μm . B: plot of average responsiveness at all thresholds for nondeprived and deprived mice. Error bars are SD. *, significance at $P < 0.02$. ND, $n = 6$; D (deprived), $n = 6$.

Plasticity of ipsilateral eye maps

A number of studies show that ipsilateral eye pathways are differentially affected by monocular deprivation (Antonini et al. 1999; Krahe et al. 2005; Tagawa et al. 2005). In light of these studies, we examined the effects of visual manipulation on ipsilateral eye cortical maps. Results for all manipulations are shown in Fig. 4A. Just as with contralateral maps, 2 wk of BD significantly reduced the strength of ipsilateral eye maps without changing their size (Fig. 4, C and D; $P = 0.035$ for responsiveness, $P = 0.18$ for area, ND vs. BD).

Depriving only the ipsilateral eye penalized ipsilateral maps to a greater degree than did BD [Fig. 4C; $P = 0.007$ ipsilateral monocular deprivation (iMD) vs. BD]. Notably, the area of cortex responding to ipsilateral eye stimulation was significantly reduced relative to normal following iMD (Fig. 4D; $P < 0.001$). iMD had no effect on any aspect of the open, contralateral eye maps (Fig. 2, $P = 0.99$ for strength and area measurements). Thus the contralateral projection was not enhanced by the loss of ipsilateral territory or strength.

The observation that ipsilateral eye maps are differentially affected by BD and iMD led us to further examine the influence of contralateral eye activity on ipsilateral eye maps. With the ipsilateral eye sutured shut, we enucleated the contralateral eye. The strength of the resulting maps was between that of maps from BD and normal mice such that there was no statistically significant difference from either [Fig. 4, A and H; $P = 0.29$ contralateral enucleation and ipsilateral monocular deprivation (cE+iMD) vs. BD; $P = 0.10$ cE+iMD vs. ND].

We then altered contralateral vision while the ipsilateral eye remained open. In agreement with other studies (Frenkel and Bear 2004; Kaneko et al. 2008a; Mrsic-Flogel et al. 2007), we found that when the contralateral eye was sutured, the strength of ipsilateral eye maps increased (Fig. 4F, $P = 0.031$ ND vs. cMD), but the size of the responsive area did not change (Fig. 4G; $P = 0.47$ for area). Enucleating the contralateral eye increased the responsiveness of the open ipsilateral eye even further and resulted in an expansion of responsive cortex (Fig. 4, F and G; $P = 0.002$ for responsiveness, $P < 0.001$ for area, ND vs. cE). This functional expansion of the ipsilateral eye's cortical territory was not accompanied by an expansion of ipsilateral eye inputs in the lateral geniculate nucleus of the thalamus (mean labeled LGN volume $\pm$ SD in ND and cE, respectively: $0.027 \pm 0.004 \text{ mm}^3$, $0.031 \pm 0.006 \text{ mm}^3$; $P = 0.248$).

Quality of vision through a sutured eyelid

To measure the quantity and quality of activity arriving through a sutured eyelid, we imaged four mice before and after an acute lid suture. For each mouse, we also acquired a map using no visual stimulus to quantify the noise floor.

These data are presented in Fig. 5. Lid suture attenuated cortical responsiveness by a mean of 63%. Notably, the response map was still preserved, whereas the retinotopic organization of this response was completely destroyed. On the other hand, mice viewing 5% contrast bars through an open eye had cortical responses that were roughly half as strong as those of mice viewing 100% contrast bars through a closed lid. Nonetheless, the retinotopic maps of mice viewing 5% bars were well organized. Thus vision through a closed lid appears to adequately drive cortex while eliminating any spatial information of the stimulus.

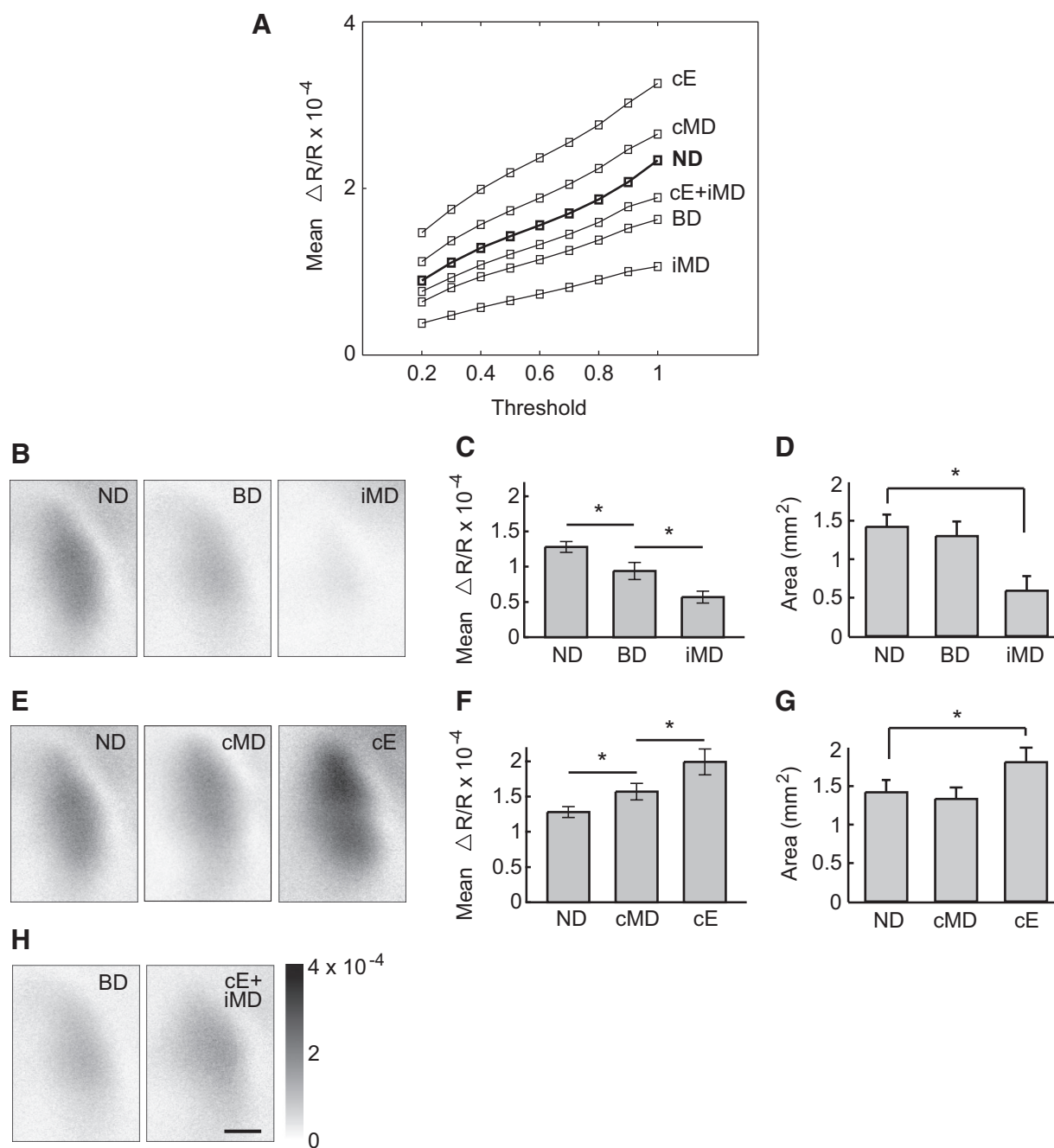


FIG. 4. Plasticity of the ipsilateral pathway in the binocular zone. *A*: strength of cortical response after each manipulation. Graph is as in Fig. 2*A*. The number of mice in each group is given below. *B*, *E*, and *H*: example ipsilateral eye magnitude maps from each visual manipulation. Abbreviations in the upper right of each image are defined below. Scale bar is 500 μ m. *C* and *F*: mean $\pm$ SD of the response magnitude for each condition measured at the 60% threshold (0.4 in *A*). *, significance. *P* values for the appropriate comparisons are presented in the text. *D* and *G*: mean $\pm$ SD of the response area in square millimeters. *, significance. *P* values for the appropriate comparisons are presented in the text. ND, $n = 8$; cMD, $n = 8$; BD, $n = 9$; iMD, $n = 9$; cE, $n = 6$; cE+iMD, $n = 8$.

Controls for orientation and spatial frequency

In the preceding studies, we used a horizontal bar of relatively high spatial frequency to elicit cortical responses. One possibility is that monocular deprivation results in a degradation of orientation tuning but that summed responses to all orientations remain strong. Another possibility is that neurons shift their optimum spatial frequency preferences toward lower spatial frequencies. To examine both of these issues, we used a contrast-modulated stochastic noise stimulus (Gandhi et al.

2008; Neill and Stryker 2008) to elicit cortical responses in normal mice and in mice that experienced 2 wk of contralateral lid suture. This stimulus contained all orientations and all spatial frequencies up to a cutoff frequency, which we set at 0.04 cycle/ $^{\circ}$ (see Supplemental Movie¹). Mice show strong visual responses over a spatial frequency range of 0.01–0.16 cycle/ $^{\circ}$ (Neill and Stryker 2008); 0.04 cpd is in the middle of

¹ The online version of this article contains supplemental data.

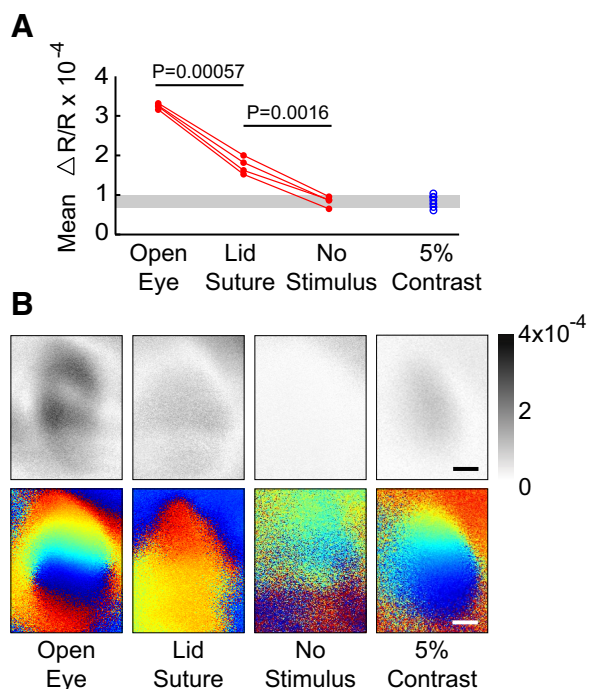


FIG. 5. How lid suture affects the cortical response to visual stimulation. **A**: the strength of evoked cortical responses before and after lid suture. Four mice viewed a drifting full-screen bar through the contralateral eye. The eyelids were then sutured and another set of maps was acquired using the same stimulus. Finally, the mouse was imaged with no stimulus to establish a noise floor. The range of this baseline noise is indicated by the gray horizontal bar. In these experiments, cortical response was measured as the peak pixel value within a user-defined region of interest. Due to a small number of random, high-intensity pixels in the no stimulus maps, the horizontal bar slightly overestimates the noise level. Lid suture attenuates cortical responsiveness by a mean of 63%. For comparison, we conducted another set of experiments in which mice viewed a similar bar at 5% contrast through open contralateral eyes. Notably, these mice had cortical responses that were roughly half as strong as those produced by 100% contrast bars through sutured lids. **B**: magnitude and phase maps after each imaging condition. The 1st 3 sets of maps are from the same mouse. Open eye magnitude maps show a robust, clearly defined area of cortical responsiveness. Open eye phase maps show smooth, continuous phase transitions, indicating the eye's discrimination of fine differences in stimulus bar elevation. After lid suture, the strength of magnitude maps diminishes, but an area of responsiveness is still evident. The more dramatic effect of lid suture is the loss of spatial resolution, evident in the phase maps. Note the complete absence of retinotopic organization. Instead, large areas of coherent phase likely represent areas of cortex co-activated by diffuse retinal illumination. Magnitude maps generated without a stimulus reveal no area of response while phase maps show no organization. Phase maps from a mouse viewing a 5% contrast bar are almost as well organized as those generated from a 100% contrast bar although the responsiveness is diminished. Scale bars are 500 μm .

that range. Relative to controls, lid suture severely degraded deprived eye cortical responses to low spatial frequency stimulation containing all orientations (Fig. 6).

DISCUSSION

We used intrinsic signal optical imaging to map changes in the strength and size of each eye's cortical representation in mice with altered visual experience. Intrinsic signal optical imaging provides a fine-grained, continuous sampling of cortical responsiveness that faithfully reflects neural activity (Masino 2003; Peterson et al. 1998). Intrinsic signal imaging reliably measures spiking activity in mouse visual cortex even

after visual deprivation (Hofer et al. 2006; Kaneko et al. 2008a,b).

Our results indicate that the plasticity of contralateral eye cortical maps is driven only by altered vision through the contralateral eye. Contralateral maps are weakened equally when both eyes are sutured shut as when only the contralateral eye is sutured. Furthermore, we find that ipsilateral eyelid suture has no effect on contralateral maps. Finally, contralateral eye suture significantly degrades cortical responsiveness in the monocular zone, an area devoid of binocular interactions.

As in the contralateral pathway, a period of ipsilateral lid suture degrades cortical responsiveness to ipsilateral eye stimulation. But interestingly, suturing both eyes shut mitigates this loss of responsiveness and prevents loss of ipsilateral territory. This result suggests that two events are at play during ipsilateral lid suture: a use-dependent loss of visual responsiveness and a further loss that is driven by the activity through the open contralateral eye.

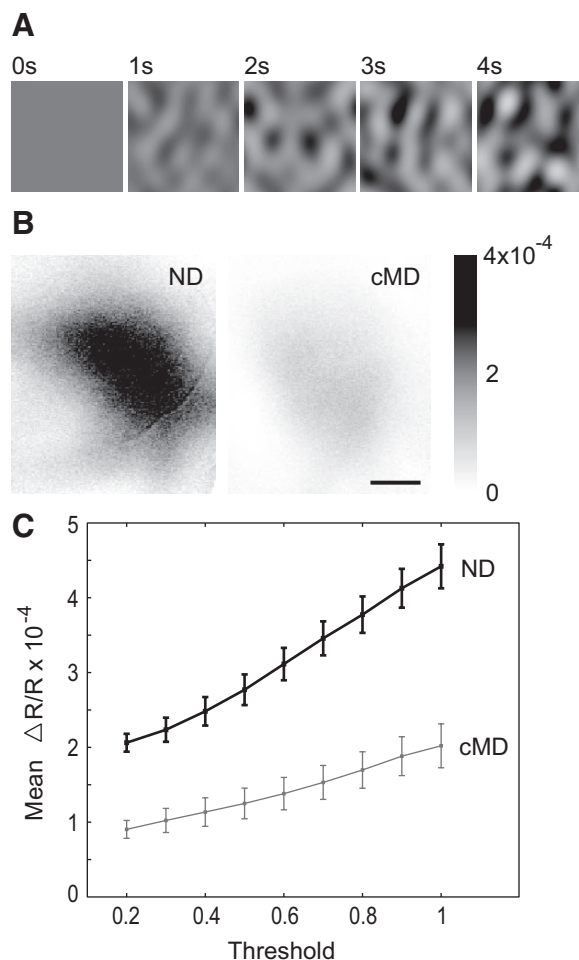


FIG. 6. Effect of monocular deprivation on contralateral eye maps – examination of all orientations with a spatial frequency cutoff of 0.04 cycle/°. **A**: representative visual stimulus over 4 s period. Mice viewed a contrast-modulated stochastic noise stimulus. **B**: example magnitude maps from contralateral eye visual stimulation using the contrast-modulated stochastic noise stimulus. Abbreviations in the upper right of each image are as in Fig. 1. Scale bar is 500 μm . **C**: mean $\pm$ SD of the response magnitude for deprived and nondeprived mice. Note the significant decay in cortical responsiveness following prolonged deprivation. ND, $n = 5$; cMD, $n = 5$.

Another way to appreciate the unique binocular plasticity of the ipsilateral pathway is to observe how ipsilateral map strength can be titrated by progressively penalizing the contralateral eye. With the ipsilateral eye open, the ipsilateral map grows stronger by suturing the contralateral eye, and stronger still by removing it. Likewise, when the ipsilateral eye is itself sutured, its map's depression can be increasingly attenuated by depriving and then removing the contralateral eye. The difference between binocular deprivation and ipsilateral deprivation with contralateral enucleation did not reach statistical significance, however.

The effects of binocular deprivation in mice are controversial. Periods of deprivation between 4 and 7 days have been variously reported to cause no effect (Frenkel and Bear 2004; Gordon et al. 1996), a strengthening effect, (Mrsic-Flogel et al. 2007), or a transient weakening in responsiveness of visual cortex (Kaneko et al. 2008b). The major difference between our findings and these others is that we employ a 2-wk period of lid suture. With both eyes sutured, there is little discrepancy in activity between the two eyes. Instead the visual cortex is driven equally poorly by unpatterned vision from the two eyes. Although this visual noise may have a slower time course in weakening cortical responsiveness than is seen when one eye remains open, our results indicate that binocular deprivation is ultimately detrimental to cortical function.

Our results force a reexamination of the standard approach for studying the molecular mechanisms of binocular plasticity in mice. We suggest that it is necessary to distinguish between molecules that regulate the experience-dependent maintenance of each eye's cortical representation and those that regulate a potentially competitive interaction between the two eyes. In most studies examining molecular mechanisms of cortical plasticity, the contralateral eye is deprived of vision, and a shift in contralateral bias is measured some days later. This approach likely results in false positives because molecules that regulate the experience-dependent maintenance of cortical maps cannot be distinguished from those that regulate competitive plasticity. In agreement with this view, a recent study has found that tumor necrosis factor- α is required for the strengthening of ipsilateral eye cortical responses after contralateral suture but plays no role in the loss of contralateral eye responses (Kaneko et al. 2008b).

The difference between the contralateral and ipsilateral pathways may explain recent observations in mice and ferrets, which both display a strong contralateral dominance. Cortical responsiveness is rapidly restored when a sutured contralateral eye is reopened (Hofer et al. 2006; Krahe et al. 2005). If, instead, the ipsilateral eye is sutured and then reopened, recovery is incomplete, and the rate of recovery is far slower, requiring protein synthesis. Recovery from an anatomical loss of ipsilateral projections would require axon growth, whereas unmasking inhibition, strengthening existing synapses, or local

synaptogenesis—three possible mechanisms for contralateral eye recovery—would be relatively rapid events.

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GRANTS

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