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*Nat Neurosci.* Author manuscript; available in PMC 2009 April 16.

Published in final edited form as:

*Nat Neurosci.* 2009 April ; 12(4): 390–392. doi:10.1038/nn.2284.

## Thalamic activity that drives visual cortical plasticity

**Monica L Linden**<sup>1,2</sup>, **Arnold J Heynen**<sup>1</sup>, **Robert H Haslinger**<sup>2,3</sup>, and **Mark F Bear**<sup>1,2</sup><sup>1</sup>*Howard Hughes Medical Institute, The Picower Institute for Learning and Memory, Cambridge, Massachusetts, USA*<sup>2</sup>*Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.*<sup>3</sup>*Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, Massachusetts, USA.*

### Abstract

Manipulations of activity in one retina can profoundly affect binocular connections in the visual cortex. Retinal activity is relayed to the cortex by the dorsal lateral geniculate nucleus (dLGN). We compared the qualities and amount of activity in the dLGN following monocular eyelid closure and monocular retinal inactivation in awake mice. Our findings substantially alter the interpretation of previous studies and define the afferent activity patterns that trigger cortical plasticity.

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The quality of sensory experience during early postnatal life has a crucial role in the development of cortical circuitry and function. In the visual system, this role has been investigated by comparing the consequences of temporary monocular eyelid closure and pharmacological inactivation of one retina with those of normal visual experience (NVE). Previous studies have shown that eyelid closure and retinal inactivation have very different effects on visual cortex<sup>1-4</sup>. A brief period of lid closure causes long-term synaptic depression (LTD) of deprived-eye responsiveness, whereas a comparable period of retinal inactivation has no effect on deprived-eye responsiveness and instead causes an increase in the responses to stimulation of the nondeprived eye (see Supplementary Fig. 1 online). Understanding how lid closure and retinal inactivation differ from one another and from NVE is of great interest because it may reveal how deprivation triggers LTD and causes visual disability. We examined this in awake mice at the age of maximal sensitivity to visual deprivation.

Bundles of electrodes were inserted in the dLGN (see Supplementary Fig. 2 and Supplementary Methods online) at the age of maximal sensitivity to monocular deprivation (~postnatal day 28, P28)<sup>5</sup>. Baseline recordings were made with the contralateral eye viewing and the ipsilateral eye occluded. Activity approximating that during NVE was recorded in response to phase-reversing sinusoidal gratings and natural scene stimuli. Unless otherwise indicated, results using grating stimuli are illustrated, as results from natural scenes did not differ qualitatively. Following the baseline recording session, we briefly anesthetized the mice and carried out eyelid closure, intraocular tetrodotoxin (TTX) injection or no manipulation (control). After >30 min of recovery from anesthesia, stimuli were presented for a second recording session.

Although eyelid closure and retinal inactivation abolished the visually evoked responses, these manipulations had no effect on spontaneous activity, and therefore had no effect on recording

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Correspondence should be addressed to M.F.B. (E-mail: [mbear@mit.edu](mailto:mbear@mit.edu)).

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session averages of firing rate (Fig. 1a,b). These findings invalidate the assumptions that visual deprivation simply reduces activity that is afferent to the cortex and that silencing the retina silences the input to cortex.

To determine whether the temporal patterning of spikes was affected by deprivation, we analyzed the distribution of interspike intervals (ISIs) before and after deprivation (Fig. 1c). Again, we were surprised to find that there was no significant effect of eyelid closure on the distribution of ISIs ( $P > 0.08$ ). Even more unexpected, however, was a shift to the left in the ISI distribution after retinal inactivation ( $P < 0.00001$ ). The shift corresponded to an increased probability of observing ISIs from 2–4 ms, suggesting that dLGN neurons tend to fire in bursts when the retina is inactivated.

Thalamic bursts have been defined in previous studies as an initial period of quiescence ( $>100$  ms) followed by two or more spikes with an ISI  $< 4$  ms<sup>6</sup>. We analyzed burst firing using this definition and found a significant increase following retinal inactivation ( $P < 0.001$ ; Fig. 2). In a subset of mice, we confirmed that increased burst firing persisted for the entire duration of retinal inactivation ( $\geq 48$  h) and returned to baseline values following TTX wash out (Fig. 2b,d and Supplementary Fig. 3 online).

Occasionally, we recorded from the ipsilateral core of the dLGN instead of our intended target of the contralateral shell. Notably, even though the retinal input to these neurons had not been changed, we found clear evidence for robust changes in the firing properties of these neurons after inactivation of the contralateral eye (Fig. 2e,f and Supplementary Fig. 4 online).

Bursting following retinal inactivation or eye enucleation has been described previously in the ferret dLGN, but these observations were made in very young animals, before natural eye opening and the developmental onset of sensitivity to monocular deprivation<sup>7</sup>. It has long been assumed that by adolescence, monocular TTX treatment simply reduces activity in the central visual system<sup>1-4,8-13</sup>. The experimental basis for this assumption can be traced to studies in anesthetized cats<sup>1,8</sup>. We therefore examined the effects of anesthesia and found that retinal inactivation significantly decreased dLGN activity in the anesthetized mouse ( $P < 0.05$ ; Fig. 2g,h and Supplementary Fig. 5 online). These findings illustrate the importance of using an awake preparation when determining the patterns of activity that drive cortical plasticity<sup>14</sup>.

None of the properties of individual spike trains (firing rate and burst percentage) differentiated NVE and eyelid closure. Therefore, we also investigated the correlative firing between simultaneously recorded neurons (Fig. 3 and Supplementary Fig. 6 online). This analysis revealed a significant decrease in simultaneously active dLGN neurons in the eyelid closed condition relative to both NVE and retinal inactivation ( $P < 0.001$ ). Thus, the manipulation of vision that triggered robust LTD in visual cortex (lid closure; see Supplementary Fig. 1) also decorrelated the input to cortex. Monocular retinal inactivation, which does not trigger response depression (Supplementary Fig. 1), actually significantly increased simultaneous firing of neuron pairs ( $P < 0.01$ ; Fig. 3b), largely as a consequence of synchronous bursting activity ( $P < 0.03$ ; Fig. 3c).

Our results show that the markedly different consequences on visual cortex of deprivation by eyelid closure and retinal inactivation<sup>1-3</sup> are accounted for by equally marked differences in dLGN activity. Although neither eyelid closure nor retinal inactivation caused a decrease in the amount of firing, lid closure resulted in a decrease of correlative firing between pairs of simultaneously recorded neurons and retinal inactivation caused an increase in thalamic bursting. These results overturn previous assumptions, provide new insight into the mechanisms that drive ocular dominance plasticity and suggest fruitful avenues for future research (see Supplementary Discussion online).

## Supplementary Material

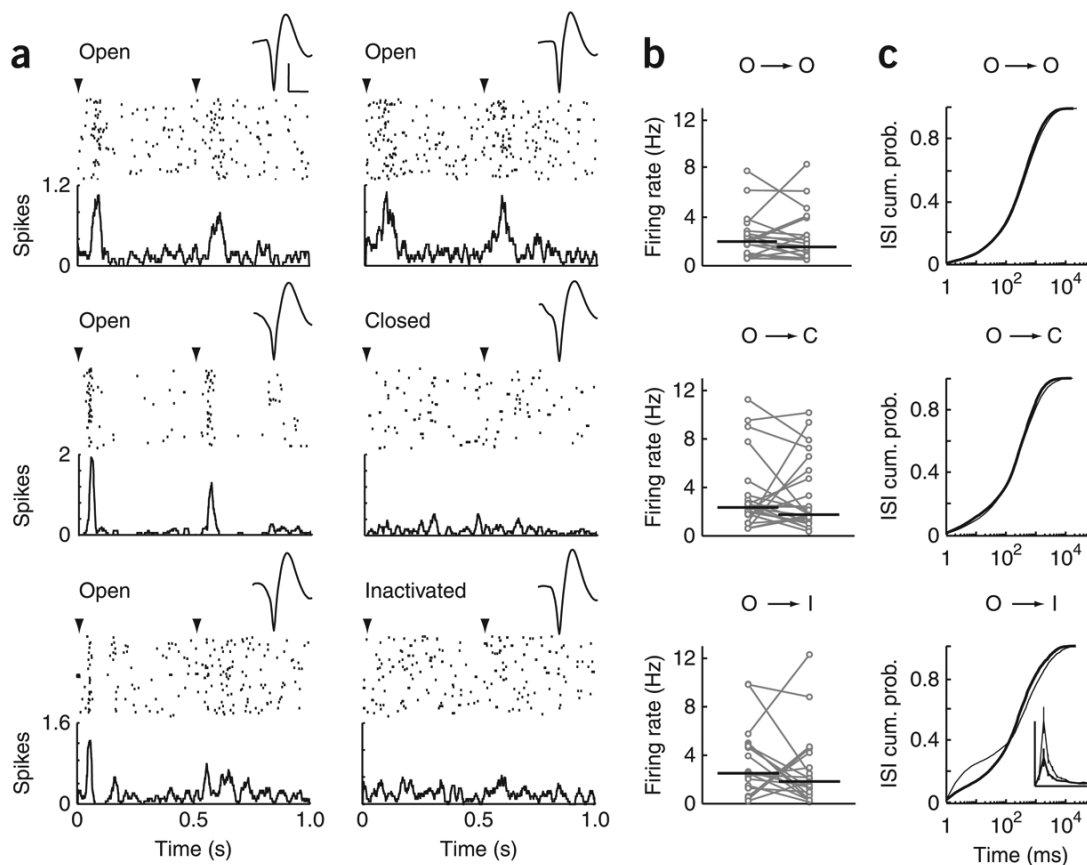
Refer to Web version on PubMed Central for supplementary material.

## ACKNOWLEDGMENTS

We thank M. Shuler, J. Coleman, M. Lamprecht, B. Blais, H. Shouval, E. Sklar, K. Oram and S. Meagher. This work was partly supported by grants from the National Eye Institute and a National Research Service Award fellowship from the US National Institute of Neurological Disorders and Stroke (M.L.L.).

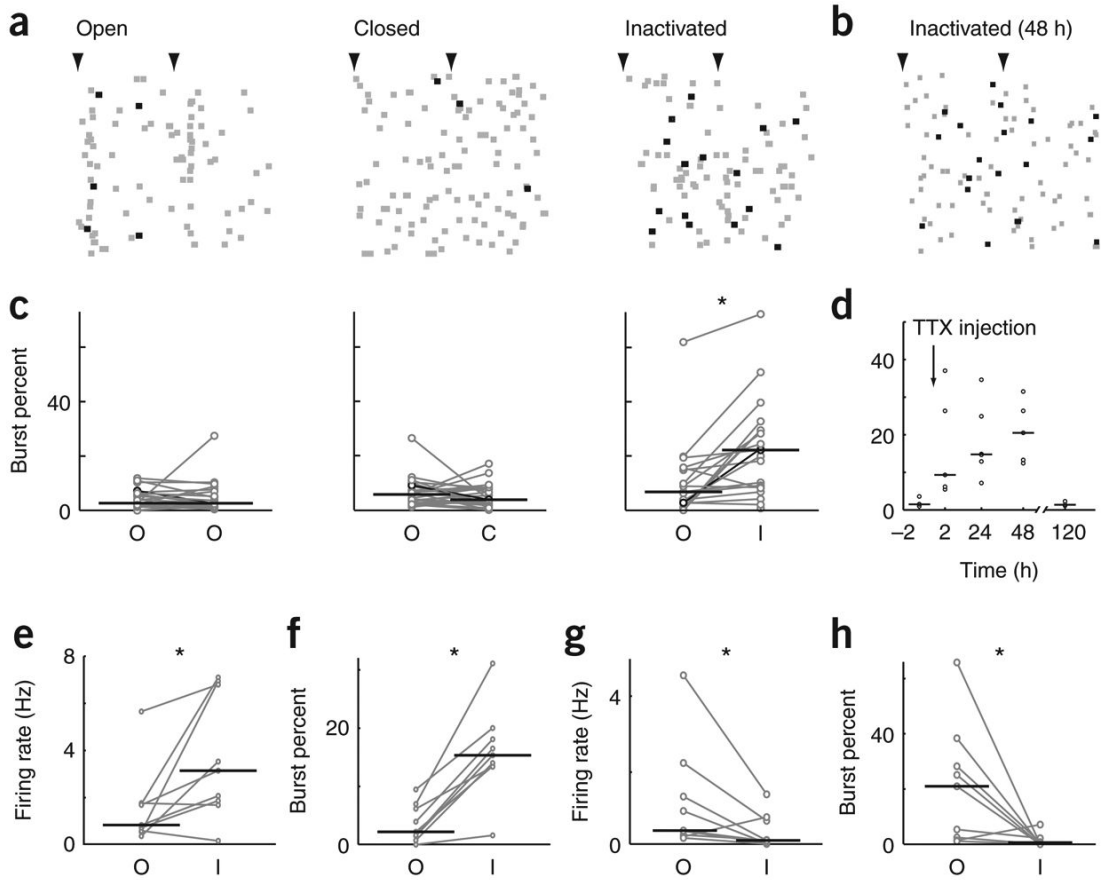
## References

1. Rittenhouse CD, Shouval HZ, Paradiso MA, Bear MF. *Nature* 1999;397:347–350. [PubMed: 9950426]
2. Heynen AJ, et al. *Nat. Neurosci* 2003;6:854–862. [PubMed: 12886226]
3. Frenkel MY, Bear MF. *Neuron* 2004;44:917–923. [PubMed: 15603735]
4. Maffei A, Turrigiano GG. *J. Neurosci* 2008;28:4377–4384. [PubMed: 18434516]
5. Gordon JA, Stryker MP. *J. Neurosci* 1996;16:3274–3286. [PubMed: 8627365]
6. Lu SM, Guido W, Sherman SM. *J. Neurophysiol* 1992;68:2185–2198. [PubMed: 1337104]
7. Weliky M, Katz LC. *Science* 1999;285:599–604. [PubMed: 10417392]
8. Stryker MP, Harris WA. *J. Neurosci* 1986;6:2117–2133. [PubMed: 3746403]
9. Greuel JM, Luhmann HJ, Singer W. *Brain Res* 1987;431:141–149. [PubMed: 3620983]
10. Catalano SM, Chang CK, Shatz CJ. *J. Neurosci* 1997;17:8376–8390. [PubMed: 9334411]
11. Caleo M, Lodovichi C, Maffei L. *Eur. J. Neurosci* 1999;11:2979–2984. [PubMed: 10457192]
12. Desai NS, Cudmore RH, Nelson SB, Turrigiano GG. *Nat. Neurosci* 2002;5:783–789. [PubMed: 12080341]
13. Young JM, et al. *Nat. Neurosci* 2007;10:887–895. [PubMed: 17529985]
14. Greenberg DS, Houweling AR, Kerr JN. *Nat. Neurosci* 2008;11:749–751. [PubMed: 18552841]



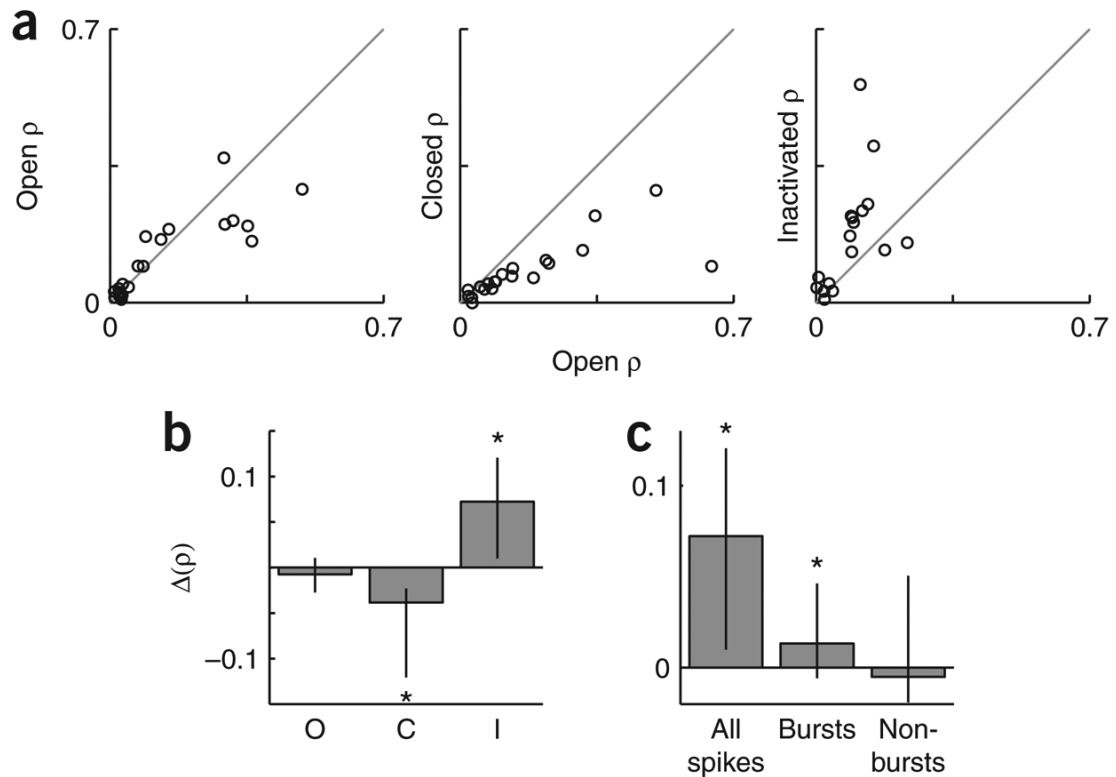
**Figure 1.**

Firing rate and ISI distributions before and after visual manipulation. **(a)** Peristimulus time histograms and raster plots from representative neurons for each experimental group. Stimuli were presented at 0 or 90°, 1-Hz phase reversing. Arrowheads in this and subsequent figures indicate time of stimulus phase reversal. Spike waveforms are recording session averages. Scale bars represent 100  $\mu$ V and 500  $\mu$ s. Left, data were obtained during baseline. Right, data were obtained after eye manipulation. Top, control group; middle, monocular eyelid closure group; bottom, retinal inactivation group. **(b)** Firing rates (recording session average) for each neuron in each group. Connected circles represent the same neuron recorded before and after eye manipulation (O, open; C, closed; I, inactivated). Black lines indicate median values (control:  $n = 22$  neurons (9 mice),  $P > 0.2$  Wilcoxon sign-rank; eyelid closure:  $n = 24$  neurons (12 mice),  $P > 0.3$ ; retinal inactivation:  $n = 19$  neurons (8 mice),  $P > 0.3$ ). See Supplementary Figure 6 for similar results with natural visual stimuli. **(c)** ISI distributions during baseline (thick black line) and after eye manipulation (thin black line). Note that retinal inactivation increased the probability of observing short ISIs ( $P < 10^{-5}$ ). Inset, probability density function (y axis, 0–0.14; x axis, 0–20 ms); the curves differ significantly from 2–4 ms ( $P < 0.01$ , Wilcoxon sign-rank).



**Figure 2.**

Analysis of bursting activity before and after visual manipulation. **(a)** Raster plots of 80 stimulus trials from representative neurons (those nearest the median) in each experimental group. Black squares represent spikes in bursts and gray squares represent non-burst spikes. **(b)** Bursting of a representative neuron 48 h after intraocular TTX injection (see also Supplementary Fig. 3). **(c)** Burst percentage for each neuron in each group. Connected circles represent the same neuron recorded before and after eye manipulation. Black lines indicate the median values (control:  $n = 22$  neurons (9 mice),  $P > 0.7$ ; eyelid closure:  $n = 24$  neurons (12 mice),  $P > 0.2$ ); retinal inactivation:  $n = 19$  neurons (8 mice),  $P < 10^{-3}$  Wilcoxon sign-rank). **(d)** Burst percentage as a function of the duration of retinal inactivation. Circles represent individual neurons. Black lines indicate the median values. At 2, 24 and 48 h, the percentage of spikes in bursts was significantly different from both the baseline and recovery (120 h) time points ( $P < 0.05$  for all comparisons, Mann-Whitney U test). The baseline and recovery time points were not significantly different ( $P > 0.7$ , Mann-Whitney U test), nor were the time points during retinal inactivation ( $P > 0.4$  for all comparisons, Mann-Whitney U test). **(e,f)** Inactivation of the contralateral eye increased firing rate and bursting of neurons in the dLGN ipsilateral core ( $n = 9$  neurons (4 mice),  $P < 0.02$  and  $0.01$ , respectively, Wilcoxon sign-rank). Data are presented as in **c** (see also Supplementary Fig. 4). **(g,h)** Neuronal firing rate and the percentage of spike in bursts decreased significantly after retinal inactivation in Nembutal-anesthetized mice ( $n = 9$  neurons (3 mice),  $P < 0.05$  and  $0.03$ , respectively, Wilcoxon sign-rank).



**Figure 3.**

Eyelid closure and retinal inactivation have opposite effects on correlative dLGN firing. **(a)** Scatter plots of the area under the cross-correlogram from pairs of simultaneously recorded neurons before and after visual manipulation for each pair of simultaneously recorded neurons. Gray line represents unity. Note that nearly all points fall below the unity line following eyelid closure (center panel), indicating a decrease in correlative firing ( $\rho$  indicates correlation coefficient). **(b)** Eyelid closure and retinal inactivation had opposite effects on spike correlation ( $P < 10^{-4}$  Kruskal-Wallis test). Bars represent the median change in area under the peak of the cross-correlogram ( $\pm 10$  ms) following visual manipulation. Error bars show the interquartile range. Eyelid closure and retinal inactivation induced significant changes in correlation (control:  $n = 22$  neuron pairs (6 mice),  $P > 0.2$  Wilcoxon sign-rank; eyelid closure:  $n = 20$  neuron pairs (6 mice),  $P < 10^{-3}$ ; retinal inactivation:  $n = 18$  neuron pairs (6 mice),  $P < 0.01$ ; see also Supplementary Fig. 6). **(c)** Bursts contributed to increased correlation following retinal inactivation. Data are represented as in **b**. The bursts group considered only the first spikes in each burst ( $n = 18$  neuron pairs (6 mice),  $P < 0.03$ ); the non-bursts group considered all spikes not contained in bursts ( $P > 0.9$ ).