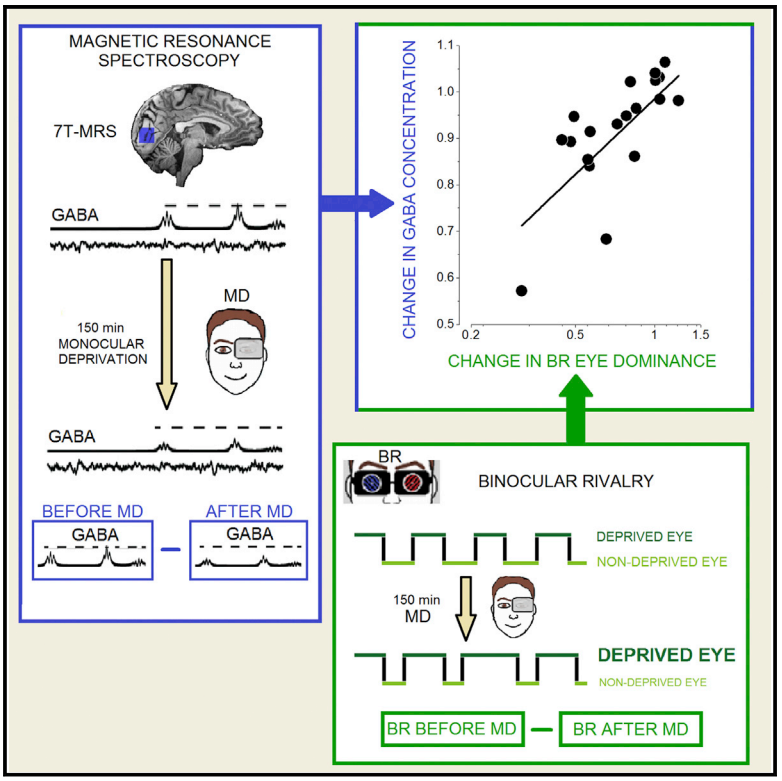
Report

Current Biology

Short-Term Monocular Deprivation Alters GABA in the Adult Human Visual Cortex

Graphical Abstract



Highlights

- In adult humans, 2.5 hr of monocular deprivation strongly boosts vision in deprived eye
- Primary visual cortex resting GABA is decreased after 2.5 hr of monocular deprivation
- The change in resting GABA strongly correlates with deprived eye perceptual boost
- A decrease in resting GABA triggers homeostatic plasticity in adult primary visual cortex

Authors

Claudia Lunghi, Uzay E. Emir, Maria Concetta Morrone, Holly Bridge

Correspondence

concetta@in.cnr.it

In Brief

Lunghi et al. show that short-term monocular deprivation drives homeostatic plasticity in adult humans, favoring input from the deprived eye. Using 7T MR spectroscopy, they show that resting GABA concentration decreases after deprivation and that the decrease in GABA strongly correlates with the individual plastic change, implying a causal effect.

Lunghi et al., 2015, Current Biology *25*, 1496–1501
June 1, 2015
http://dx.doi.org/10.1016/j.cub.2015.04.021

CellPress

Current Biology
Report

Short-Term Monocular Deprivation Alters GABA in the Adult Human Visual Cortex

Claudia Lunghi,[1,2,5] Uzay E. Emir,[3,5] Maria Concetta Morrone,[1,4,*] and Holly Bridge[3]
[1]Department of Translational Research on New Technologies in Medicine and Surgery, University of Pisa, 56126 Pisa, Italy
[2]Institute of Neuroscience, CNR, 56124 Pisa, Italy
[3]FMRIB, University of Oxford, Oxford, Oxfordshire OX3 9DU, UK
[4]Scientific Institute Stella Maris (IRCSS), Calambrone, 56018 Pisa, Italy
[5]Co-first author
*Correspondence: concetta@in.cnr.it
http://dx.doi.org/10.1016/j.cub.2015.04.021

SUMMARY

Neuroplasticity is a fundamental property of the nervous system that is maximal early in life, within the critical period [1–3]. Resting GABAergic inhibition is necessary to trigger ocular dominance plasticity and to modulate the onset and offset of the critical period [4, 5]. GABAergic inhibition also plays a crucial role in neuroplasticity of adult animals: the balance between excitation and inhibition in the primary visual cortex (V1), measured at rest, modulates the susceptibility of ocular dominance to deprivation [6–10]. In adult humans, short-term monocular deprivation strongly modifies ocular balance, unexpectedly boosting the deprived eye, reflecting homeostatic plasticity [11, 12]. There is no direct evidence, however, to support resting GABAergic inhibition in homeostatic plasticity induced by visual deprivation. Here, we tested the hypothesis that GABAergic inhibition, measured at rest, is reduced by deprivation, as demonstrated by animal studies. GABA concentration in V1 of adult humans was measured using ultra-high-field 7T magnetic resonance spectroscopy before and after short-term monocular deprivation. After monocular deprivation, resting GABA concentration decreased in V1 but was unaltered in a control parietal area. Importantly, across participants, the decrease in GABA strongly correlated with the deprived eye perceptual boost measured by binocular rivalry. Furthermore, after deprivation, GABA concentration measured during monocular stimulation correlated with the deprived eye dominance. We suggest that reduction in resting GABAergic inhibition triggers homeostatic plasticity in adult human V1 after a brief period of abnormal visual experience. These results are potentially useful for developing new therapeutic strategies that could exploit the intrinsic residual plasticity of the adult human visual cortex.

RESULTS

Binocular Rivalry Dynamics Change after Monocular Deprivation

We tested binocular rivalry between oriented gratings in 19 healthy volunteers (monocular deprivation group, mean age 24.3 ± 5.4 years) before and after 150 min of monocular deprivation. Before deprivation (Figure 1B), all observers showed similar durations in which they perceived the stimulus presented to one or the other eye (called mean phase duration), as shown by the scatter of the individual subject's data around the unity line in Figure 1B. The average dominant to non-dominant eye duration ratio was 1.23 ± 0.03 (Figure 1D), indicating a slight preference for one eye. Consistent with previous reports [11, 12], 150 min of monocular deprivation of the dominant eye resulted in increased perceptual dominance of this eye during binocular rivalry (Figure 1C; Figure 1D, average dominant to non-dominant eye mean phase duration ratio: 1.82 ± 0.16). The increase in eye-dominance ratio is highly significant (paired t test, $t(18) = 3.48$, $p = 0.003$). The red symbols in Figures 1B and 1C show the data of control subjects (control group, n = 7, mean age 26.2 ± 6 years) that followed the same procedure but did not undergo monocular deprivation (average dominant to non-dominant eye mean phase duration ratio: first session, 1.32 ± 0.09; second session, 1.27 ± 0.1). The procedure of performing the binocular rivalry task twice, therefore, did not induce any change in performance.

Resting GABA Concentration Decreases in V1 after Monocular Deprivation

Magnetic resonance (MR) spectra were acquired at 7T from an occipital voxel ($2 \times 2 \times 2$ cm^3), centered bilaterally on the calcarine sulcus (visual cortex, V1), and a control voxel of the same size, centered on the bilateral posterior cingulate cortex (PCC). An example spectrum is shown in Figure 2A, and the average spectrum from all participants and conditions can be seen in Figure S1. A diagram of the experimental paradigm is shown in Figure 1A: each observer participated in two magnetic resonance spectroscopy (MRS) sessions separated by a 150-min interval during which the main group of observers wore a translucent eye patch over the dominant eye (monocular deprivation group). GABA levels (quantified using LCModel [13]) were

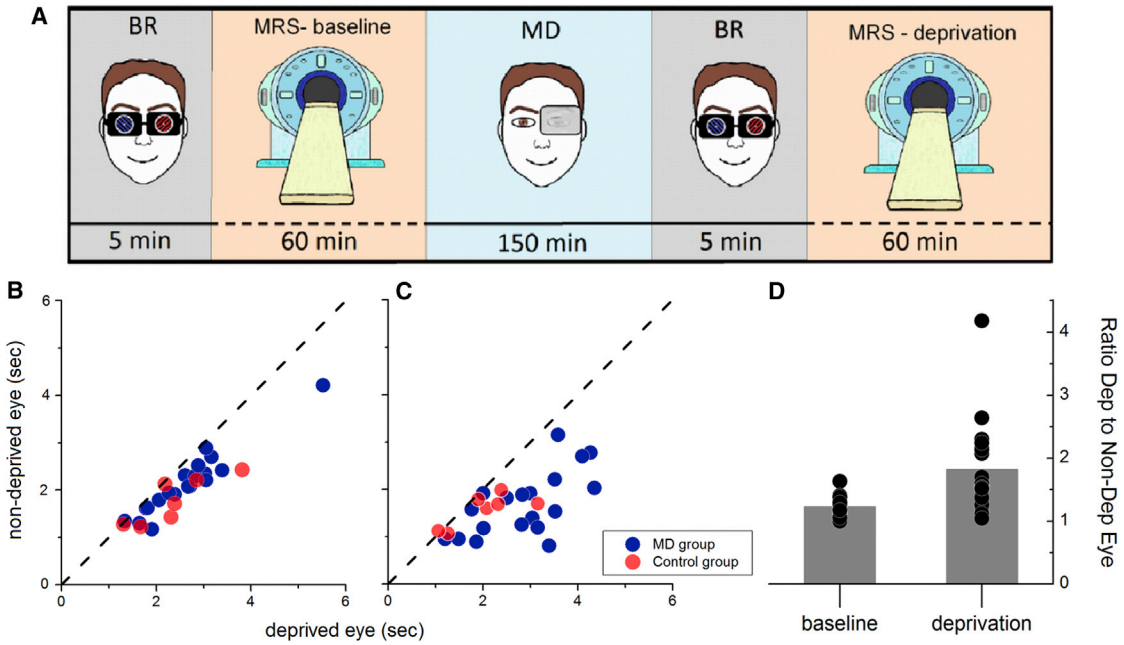


Figure 1. Experimental Design and Psychophysical Measures of Binocular Rivalry

(A) The experiment timeline consists of a baseline behavioral measure of binocular rivalry followed by a "baseline" MRS session. After 150 min of monocular deprivation, behavioral data were acquired again followed by a "deprivation" MRS session.

(B) The behavioral effect of monocular deprivation. At baseline, one eye slightly dominates perception, as indicated by higher mean phase duration

(C) Blue symbols are the individual mean phase durations following monocular deprivation, and the mean phase duration is increased in the deprived eye and decreased in the non-deprived eye, leading to the points lying further from the unity line. The red points show data from seven subjects that did not undergo deprivation but performed the task twice with a 150-min interval.

(D) Average of the ratio between deprived and non-deprived eye mean phase duration at baseline and following deprivation.

measured during four different viewing conditions: eyes closed, non-deprived eye stimulated, deprived eye stimulated, and eyes open (see Supplemental Experimental Procedures for further information about MRS acquisition and analysis).

Figure 2C shows the concentration of GABA:H_2O, and Figure 2D shows the more standard normalized concentration of GABA:tNAA acquired before and after deprivation while observers kept their eyes closed (this is considered to be a measure of resting GABA level). A significant decrease in concentration was found both for GABA:H_2O (paired-samples t test: $t(18) = 2.57$, $p = 0.019$) and for GABA:tNAA (paired-samples t test: $t(18) = 2.9$, $p = 0.009$) concentration (see Figure S3 for additional bootstrap statistics on two independent samples of subjects). The decrease in resting GABA concentration following monocular deprivation is also evident from inspection of the LCModel fits for the GABA spectra, examples of which are shown in Figures 2A and 2B. Resting GABA concentrations for all subjects are reported in Table S1. Although the primary hypothesis is a reduction of resting GABA, a non-significant decrease in GABA:H_2O and GABA:tNAA concentration was observed between pre- and post-deprivation measurements in the other viewing conditions (see Figure S4). That the effect of GABA reduction is more easily measurable during rest is to be expected since GABA is believed to play a role in many aspects of early visual processing [14]. The strength of these inhibitory interactions elicited by the stimuli may mask any effects of deprivation on GABA. No difference in spectral linewidth is observed across monocular deprivation, indicating no major blood-oxygenation-level-dependent (BOLD) effect on GABA quantification [15].

The significant decrease of both resting GABA:H_2O and resting GABA:tNAA is about 8% (one-sample t test H_0 X $\neq$ 1, Bonferroni corrected $\alpha = 0.0125$; GABA:H_2O: $t(18) = 2.89$, $p = 0.01$; GABA:tNAA: $t(18) = 2.98$, $p = 0.008$) (Figure 3, black bars). Furthermore, the decrease is specific for the V1 voxel, and it is not present for a control voxel positioned in PCC (Figure 3, etched bars; one-sample t test H_0 X $\neq$ 1; GABA:H_2O: $t(12) = 1.29$, $p = 0.22$; GABA:tNAA: $t(12) = 1.21$, $p = 0.25$). The solid gray bars of Figure 3 show the GABA:H_2O and the GABA:tNAA ratios for the V1 voxel during the control experiment when there is no monocular deprivation. While there is a trend for increased GABA:H_2O in the later MRS session, the ratios do not differ significantly from one (one-sample t test H_0 X $\neq$ 1; GABA:H_2O: $t(6) = 1.65$, $p = 0.15$; GABA:tNAA: $t(6) = 1.7$, $p = 0.14$). Furthermore, in each case, the GABA ratio in the main experiment is significantly lower than that measured from the PCC (independent-samples t test, GABA:H_2O: Bonferroni corrected $\alpha = 0.0167$, $t(30) = 2.78$, $p = 0.01$; GABA:tNAA: Bonferroni corrected $\alpha = 0.0167$, $t(30) = 2.76$, $p = 0.01$) and from V1 in the control experiment (GABA:H_2O: Bonferroni corrected $\alpha = 0.0167$, $t(24) = 3.31$, $p = 0.003$; GABA:tNAA: Bonferroni corrected $\alpha = 0.0167$, $t(24) = 3.43$, $p = 0.002$).

Taken together, these results indicate that monocular deprivation induces a change in resting GABA that is specific to V1 and

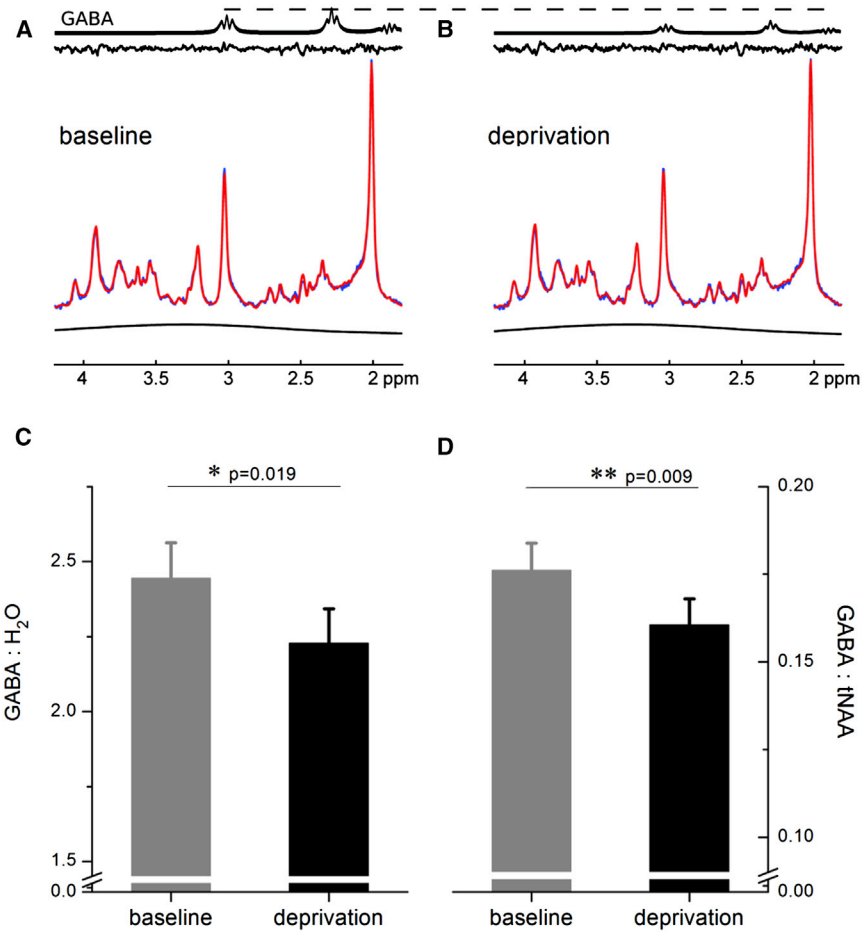


Figure 2. Effect of Monocular Deprivation on Resting GABA Concentration in the Visual Cortex

(A and B) An example spectrum for one subject and an example LCModel fit for GABA:H_2O measured before (A) and after (B) deprivation. Note the decrease of peak amplitude of GABA:H_2O spectra after deprivation (top row).

(C) Mean GABA:H_2O concentrations across subjects measured before (gray bar) and after (black bar) deprivation.

(D) Mean GABA:tNAA concentrations across subjects measured before (gray bar) and after (black bar) deprivation. Error bars represent SEM. See Supplemental Information for further details about GABA quantification and spectral quality.

does not depend on performing the behavioral task and the scanning procedure twice.

Decrease in Resting GABA Concentration Strongly Correlates with Changes in Binocular Rivalry

Having shown both a behavioral change using binocular rivalry dominance and a reduction in resting GABA concentration in visual cortex following monocular deprivation, we measured the relationship between these changes. For each subject, the ratio of deprived and non-deprived eye balance in phase duration observed before and after monocular deprivation (deprivation index; Equation 1 in Supplemental Experimental Procedures) was correlated with the ratio of resting GABA:H_2O (Figure 3C) and GABA:tNAA (Figure 3F) measured after and before deprivation. Changes in both GABA:H_2O and GABA:tNAA concentration correlated significantly with the change in perceptual predominance of the deprived eye during binocular rivalry (GABA:H_2O, Figure 3C; Spearman's rank correlation coefficient rho = 0.78, two-tailed exact permutation test $p < 0.001$, confidence intervals [CIs], Fisher's Z transformed, CI = 0.38–0.93; GABA:tNAA, Figure 3F; rho = 0.62, $p = 0.006$, CI = 0.23–0.84). These strong correlations indicate that the greater the behavioral plasticity effect, the greater the decrease of resting GABA, suggesting a link between the two measures as previously demonstrated in animals [6–10].

GABA Concentration during Monocular Stimulation Correlates with Eye Dominance after Deprivation

The individual effect of plasticity can be indirectly measured by the change in ocular dominance of binocular rivalry after deprivation. The previous results indicate that GABAergic inhibition is decreased at rest, suggesting the potential for increased neuronal responses during visual stimulation, predicted to be stronger in observers showing greater plasticity. In agreement with this prediction, we found that, after monocular deprivation, the concentration of both GABA:H_2O and GABA:tNAA measured during monocular stimulation (Figure 4) correlated with eye dominance (ratio between mean phase duration measured after monocular deprivation). When the non-deprived eye was stimulated, correlation of both GABA:H_2O (rho = −0.51 p = 0.038, CI = 0.039–0.795) and GABA:tNAA (rho = −0.56, p = 0.022, CI = 0.026–0.819) with rivalry was strong. Similar results were obtained when the deprived eye was stimulated (correlation of GABA:H_2O with rivalry: rho = −0.5, p = 0.043, CI = 0.026–0.79; correlation of GABA:tNAA with rivalry: rho = −0.53, p = 0.035, CI = 0.053–0.8).

DISCUSSION

By combining MRS with psychophysical measures of eye dominance, we have demonstrated the importance of GABAergic mechanisms for homeostatic plasticity in adult humans. Specifically, we report two important findings: first, resting GABA concentration decreases in visual cortex of adult humans after 150 min of monocular deprivation; second, and more importantly, there was a high correlation between a reduction in GABA concentration in the visual cortex and the perceptual boost of the deprived eye induced by monocular deprivation. This indicates a possible functional role of the neurochemical change in mediating the perceptual boost of the deprived eye.

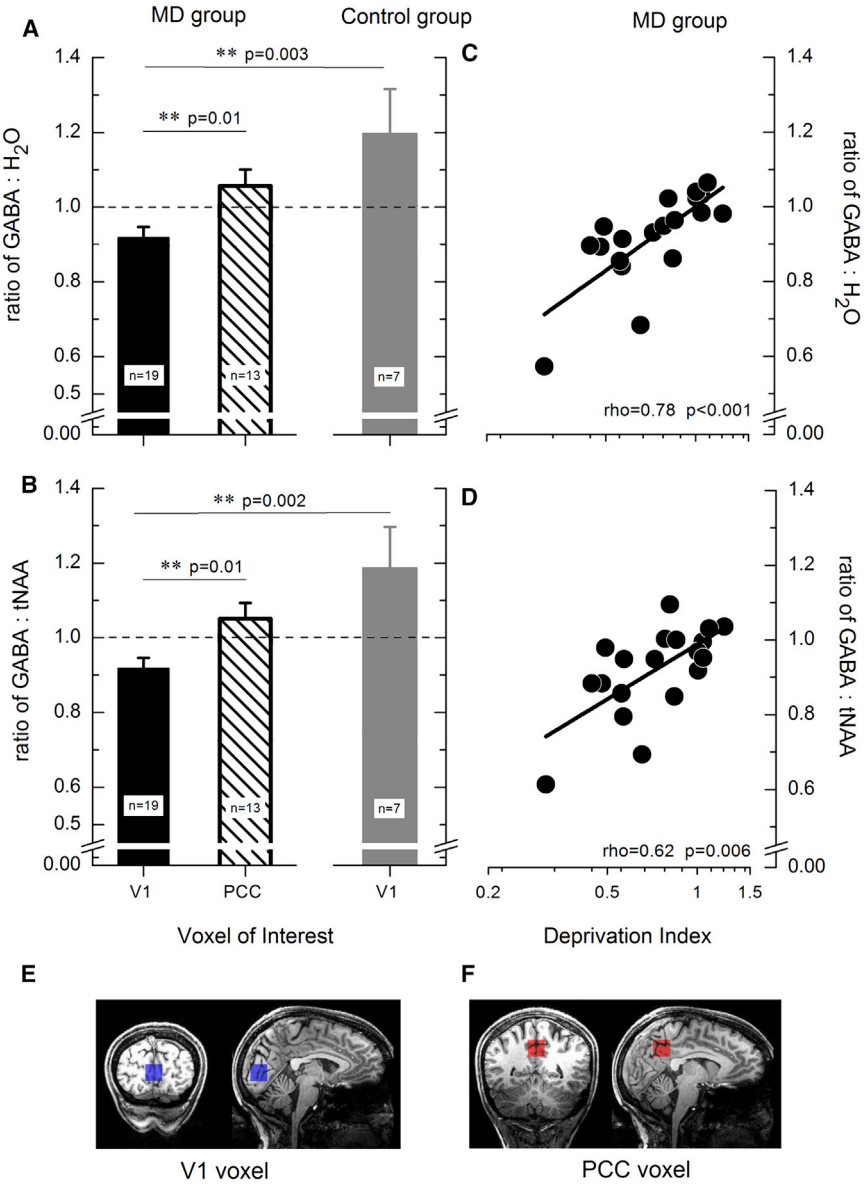


Figure 3. Decrease in Resting GABA Concentration Following Monocular Deprivation and Correlation with Change in Binocular Rivalry Eye Dominance

(A) Ratio of resting GABA:H_2O measured after and before monocular deprivation in visual cortex (black bar) and PCC (etched bar) and the ratio of resting GABA:H_2O measured in the second and first scan in the visual cortex for the control group of observers (gray bar). Error bars represent SEM.

(B) Same as (A), but for GABA:tNAA.

(C) Correlation of GABA:H2O ratio measured after and before monocular deprivation in visual cortex with the change in ratio of dominance of the patched eye (deprivation index) (see Equation 1 in Supplemental Experimental Procedures).

(D) Same as (C), but for GABA:tNAA.

(E) Location of V1 voxel from which MRS data were acquired.

(F) Location of PCC voxel from which MRS data were acquired.

Intracortical balance between excitation and inhibition plays a critical role in mediating experience-dependent plasticity during development [10]. In particular, the maturation and activity of the GABAergic inhibitory interneurons parvalbumin (PV)-expressing basket cells regulates ocular dominance plasticity [20, 21]. In juvenile mice, 1 day of monocular deprivation induces a transient reduction of responsiveness in these PV cells [22]. Furthermore, studies manipulating the balance between intracortical excitation and inhibition, either by increasing excitation [7, 8] or decreasing inhibition [6], have suggested that similar mechanisms could act in the adult brain (reviewed in [10]). There is, however, no direct evidence for a reduction of inhibitory responses during visual plasticity in adult animals or direct evidence of ocular dominance plasticity after short-term visual deprivation, as observed here. Indirect evidence in support of a role for GABAergic inhibition in human visual cortex plasticity comes from administration of benzodiazepine, which potentiates GABAergic inhibition and has been shown to block plasticity induced by light deprivation, as measured by decreased transcranial magnetic stimulation phosphene thresholds [23].

Our result of a homeostatic boost of the deprived eye induced by a few hours of monocular deprivation is surprising, particularly given that the modulation occurs at such short timescales. In mice, only after several days of monocular deprivation during the critical period is there an increase in the spontaneous neuronal responses of a subset of cells devoted to the deprived eye [16]. This is a compensatory neural reaction that dynamically readjusts neuronal excitability in order to keep the average neural activity constant, known as homeostatic plasticity [17]. Interestingly, homeostatic plasticity, which involves changes in the balance between excitation and inhibition at the synaptic level [18], has never been observed in the intact adult visual cortex [19] or after short-term monocular deprivation. We therefore provide the first direct evidence in favor of a specific, important role of resting GABAergic inhibition in driving homeostatic plasticity in adult human visual cortex.

In adults, neural plasticity has been consistently induced in structures such as the hippocampus [24] and the primary somatosensory cortex [25], and this type of plasticity appears to persist throughout life. Furthermore, changes in GABA concentration in adult human primary motor cortex have been shown following motor learning [26, 27], pointing to a pivotal role of intracortical inhibition in mediating motor cortical plasticity. The fact that we found a modulation of GABAergic balance in a cortical region that primarily comprises V1 is particularly

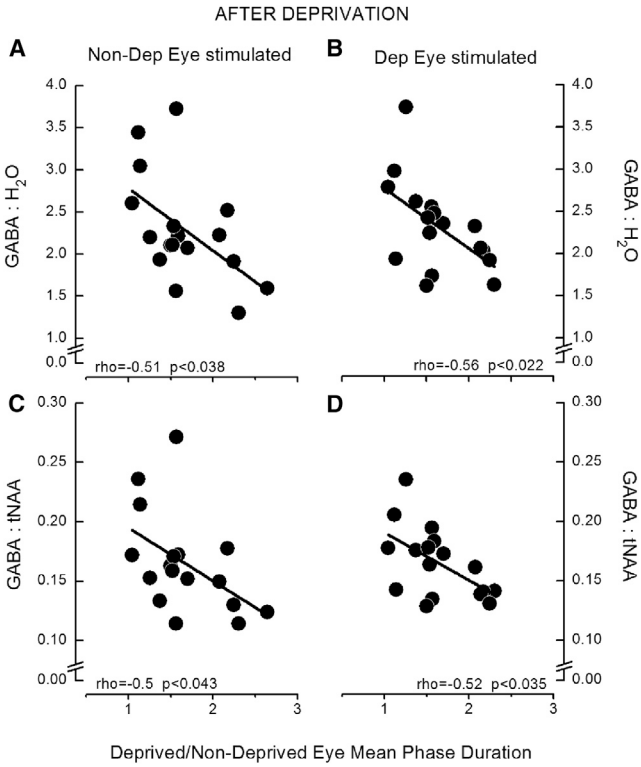


Figure 4. Correlation between Eye Dominance and GABA Concentration during Monocular Stimulation Measured after Deprivation

(A and B) The concentration of GABA:H_2O measured after deprivation during stimulation of the non-deprived (A) and deprived (B) eye is plotted against the perceptual index of eye dominance (ratio between mean phase duration of the stimulus presented to the deprived and non-deprived eye during binocular rivalry).

(C and D) Same as (A) and (B) but for GABA:tNAA concentrations.

important, as it indicates that the types of plasticity seen in other adult neural systems (e.g., long-term potentiation or long-term depression [28]) may also be present in the visual cortex.

In recent years, several functional MRS studies at ultra-high field have demonstrated small, but significant, variations in the concentration of some brain metabolites in the activated human visual cortex during prolonged visual stimulation [29–31]. These studies, however, have not found a significant change in GABA concentration during visual stimulation [31, 32]. Here, we show that GABA measured in response to visual stimulation is a sensitive measure to probe plasticity. Ocular dominance after deprivation is a measure of plasticity, and it is interesting that it correlates with GABA concentration during stimulation of either the deprived or non-deprived eye. The most straightforward interpretation of this finding is that the reduction of resting GABA leads to a local increase in cortical excitability (resting GABA concentration has been previously shown to correlate with BOLD responsiveness [33, 34]). This finding is supported by the demonstration that GABA concentration measured during visual stimulation correlates negatively with the switching rate of three different forms of bistable perception (binocular rivalry, motion-induced blindness, and structure from motion [35]), simulating the effect of pharmacological stimulation of $GABA_A$ receptors [35]. It is plausible that the reduction of resting GABA could also induce a reduction of interocular suppression during stimulation (multiplicative inhibition). This is consistent with animal studies showing that application of the GABA antagonist bicuculline abolishes interocular suppression [36, 37] and with the suggestion that the dynamics of interocular suppression determine binocular rivalry at a cortical level [38].

We previously found that, following 150 min of monocular deprivation, the perceptual advantage of the deprived eye observed during binocular rivalry was accompanied by a boost in apparent contrast [11], suggesting an involvement of contrast gain control mechanisms in mediating short-term homeostatic plasticity. The decreased GABA concentration that we found in V1 is consistent with our hypothesis of deprivation upregulating homeostatic contrast gain of the deprived eye. Evidence from animal studies suggests that contrast gain is GABA mediated in V1 [39–41]. Interestingly, contrast gain control mechanisms have been shown to modulate neuronal activity in humans (measured both by visual evoked potentials [40] and BOLD [42]) in a multiplicative way and to be involved in regulating both the dynamics of binocular rivalry [43] and eye dominance [44] during binocular combination (binocular combination also being altered after monocular deprivation in adult humans [45]). Furthermore, as monocular patching of the fellow eye is currently used as treatment for amblyopia in children, our results suggest that GABAergic inhibition could be involved in the plastic recovery of acuity in the amblyopic eye observed after occlusion therapy. Taken together, our results show a critical role for GABAergic inhibition in triggering visual plasticity, thus suggesting potential for medium-term intervention for disorders of binocular vision even beyond the critical period in humans.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, four figures, and one table and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2015.04.021.

AUTHOR CONTRIBUTIONS

C.L., M.C.M., and H.B. designed the research. U.E.E. and C.L. performed MRS and analyzed the data. M.C.M. and H.B. supervised the project. All authors wrote the paper.

ACKNOWLEDGMENTS

This research was supported by the European Research Council under the European Union's Seventh Framework Programme (FPT/2007-2013) under grant agreement #338866 (M.C.M. and C.L.) and by the Royal Society (H.B. is a Royal Society University Research Fellow). We would like to thank Clark Lemke and Adam Chekroud for help with the data collection and David Charles Burr for comments and helpful discussion.

Received: September 7, 2014
Revised: February 24, 2015
Accepted: April 13, 2015
Published: May 21, 2015

REFERENCES

1. Wiesel, T.N. (1982). Postnatal development of the visual cortex and the influence of environment. Nature *299*, 583–591.

2. Berardi, N., Pizzorusso, T., and Maffei, L. (2000). Critical periods during sensory development. Curr. Opin. Neurobiol. *10*, 138–145.
3. Pascual-Leone, A., Amedi, A., Fregni, F., and Merabet, L.B. (2005). The plastic human brain cortex. Annu. Rev. Neurosci. *28*, 377–401.
4. Fagiolini, M., and Hensch, T.K. (2000). Inhibitory threshold for critical-period activation in primary visual cortex. Nature *404*, 183–186.
5. Hensch, T.K., Fagiolini, M., Mataga, N., Stryker, M.P., Baekkeskov, S., and Kash, S.F. (1998). Local GABA circuit control of experience-dependent plasticity in developing visual cortex. Science *282*, 1504–1508.
6. Harauzov, A., Spolidoro, M., DiCristo, G., De Pasquale, R., Cancedda, L., Pizzorusso, T., Viegi, A., Berardi, N., and Maffei, L. (2010). Reducing intracortical inhibition in the adult visual cortex promotes ocular dominance plasticity. J. Neurosci. *30*, 361–371.
7. Maya Vetencourt, J.F., Sale, A., Viegi, A., Baroncelli, L., De Pasquale, R., O'Leary, O.F., Castrén, E., and Maffei, L. (2008). The antidepressant fluoxetine restores plasticity in the adult visual cortex. Science *320*, 385–388.
8. Morishita, H., Miwa, J.M., Heintz, N., and Hensch, T.K. (2010). Lynx1, a cholinergic brake, limits plasticity in adult visual cortex. Science *330*, 1238–1240.
9. Pizzorusso, T., Medini, P., Berardi, N., Chierzi, S., Fawcett, J.W., and Maffei, L. (2002). Reactivation of ocular dominance plasticity in the adult visual cortex. Science *298*, 1248–1251.
10. Heimel, J.A., van Versendaal, D., and Levelt, C.N. (2011). The role of GABAergic inhibition in ocular dominance plasticity. Neural Plast. *2011*, 391763.
11. Lunghi, C., Burr, D.C., and Morrone, C. (2011). Brief periods of monocular deprivation disrupt ocular balance in human adult visual cortex. Curr. Biol. *21*, R538–R539.
12. Lunghi, C., Burr, D.C., and Morrone, M.C. (2013). Long-term effects of monocular deprivation revealed with binocular rivalry gratings modulated in luminance and in color. J. Vis. *13*, 1.
13. Provencher, S.W. (2001). Automatic quantitation of localized in vivo 1H spectra with LCModel. NMR Biomed. *14*, 260–264.
14. Haider, B., Häusser, M., and Carandini, M. (2013). Inhibition dominates sensory responses in the awake cortex. Nature *493*, 97–100.
15. Bednařík, P., Tkáč, I., Giove, F., DiNuzzo, M., Deelchand, D.K., Emir, U.E., Eberly, L.E., and Mangia, S. (2015). Neurochemical and BOLD responses during neuronal activation measured in the human visual cortex at 7 Tesla. J. Cereb. Blood Flow Metab. *35*, 601–610.
16. Mrsic-Flogel, T.D., Hofer, S.B., Ohki, K., Reid, R.C., Bonhoeffer, T., and Hübener, M. (2007). Homeostatic regulation of eye-specific responses in visual cortex during ocular dominance plasticity. Neuron *54*, 961–972.
17. Turrigiano, G.G., and Nelson, S.B. (2004). Homeostatic plasticity in the developing nervous system. Nat. Rev. Neurosci. *5*, 97–107.
18. Maffei, A., and Turrigiano, G.G. (2008). Multiple modes of network homeostasis in visual cortical layer 2/3. J. Neurosci. *28*, 4377–4384.
19. Ranson, A., Cheetham, C.E., Fox, K., and Sengpiel, F. (2012). Homeostatic plasticity mechanisms are required for juvenile, but not adult, ocular dominance plasticity. Proc. Natl. Acad. Sci. USA *109*, 1311–1316.
20. Huang, Z.J., Kirkwood, A., Pizzorusso, T., Porciatti, V., Morales, B., Bear, M.F., Maffei, L., and Tonegawa, S. (1999). BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. Cell *98*, 739–755.
21. Fagiolini, M., Fritschy, J.M., Löw, K., Möhler, H., Rudolph, U., and Hensch, T.K. (2004). Specific GABAA circuits for visual cortical plasticity. Science *303*, 1681–1683.
22. Kuhlman, S.J., Olivas, N.D., Tring, E., Ikrar, T., Xu, X., and Trachtenberg, J.T. (2013). A disinhibitory microcircuit initiates critical-period plasticity in the visual cortex. Nature *501*, 543–546.
23. Boroojerdi, B., Battaglia, F., Muellbacher, W., and Cohen, L.G. (2001). Mechanisms underlying rapid experience-dependent plasticity in the human visual cortex. Proc. Natl. Acad. Sci. USA *98*, 14698–14701.
24. Gu, Y., Janoschka, S., and Ge, S. (2013). Neurogenesis and hippocampal plasticity in adult brain. Curr. Top. Behav. Neurosci. *15*, 31–48.
25. Karni, A., Meyer, G., Jezzard, P., Adams, M.M., Turner, R., and Ungerleider, L.G. (1995). Functional MRI evidence for adult motor cortex plasticity during motor skill learning. Nature *377*, 155–158.
26. Floyer-Lea, A., Wylezinska, M., Kincses, T., and Matthews, P.M. (2006). Rapid modulation of GABA concentration in human sensorimotor cortex during motor learning. J. Neurophysiol. *95*, 1639–1644.
27. Stagg, C.J., Bachtiar, V., and Johansen-Berg, H. (2011). The role of GABA in human motor learning. Curr. Biol. *21*, 480–484.
28. Kirkwood, A., and Bear, M.F. (1994). Hebbian synapses in visual cortex. J. Neurosci. *14*, 1634–1645.
29. Mangia, S., Tkác, I., Gruetter, R., Van de Moortele, P.F., Maraviglia, B., and Uğurbil, K. (2007). Sustained neuronal activation raises oxidative metabolism to a new steady-state level: evidence from 1H NMR spectroscopy in the human visual cortex. J. Cereb. Blood Flow Metab. *27*, 1055–1063.
30. Mangia, S., Tkác, I., Logothetis, N.K., Gruetter, R., Van de Moortele, P.F., and Uğurbil, K. (2007). Dynamics of lactate concentration and blood oxygen level-dependent effect in the human visual cortex during repeated identical stimuli. J. Neurosci. Res. *85*, 3340–3346.
31. Schaller, B., Mekle, R., Xin, L., Kunz, N., and Gruetter, R. (2013). Net increase of lactate and glutamate concentration in activated human visual cortex detected with magnetic resonance spectroscopy at 7 tesla. J. Neurosci. Res. *91*, 1076–1083.
32. Lin, Y., Stephenson, M.C., Xin, L., Napolitano, A., and Morris, P.G. (2012). Investigating the metabolic changes due to visual stimulation using functional proton magnetic resonance spectroscopy at 7cT. J. Cereb. Blood Flow Metab. *32*, 1484–1495.
33. Donahue, M.J., Near, J., Blicher, J.U., and Jezzard, P. (2010). Baseline GABA concentration and fMRI response. Neuroimage *53*, 392–398.
34. Muthukumaraswamy, S.D., Edden, R.A., Jones, D.K., Swettenham, J.B., and Singh, K.D. (2009). Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans. Proc. Natl. Acad. Sci. USA *106*, 8356–8361.
35. van Loon, A.M., Knapen, T., Scholte, H.S., St John-Saaltink, E., Donner, T.H., and Lamme, V.A. (2013). GABA shapes the dynamics of bistable perception. Curr. Biol. *23*, 823–827.
36. Sengpiel, F., Jirmann, K.U., Vorobyov, V., and Eysel, U.T. (2006). Strabismic suppression is mediated by inhibitory interactions in the primary visual cortex. Cereb. Cortex *16*, 1750–1758.
37. Sengpiel, F., and Vorobyov, V. (2005). Intracortical origins of interocular suppression in the visual cortex. J. Neurosci. *25*, 6394–6400.
38. Sengpiel, F., Blakemore, C., and Harrad, R. (1995). Interocular suppression in the primary visual cortex: a possible neural basis of binocular rivalry. Vision Res. *35*, 179–195.
39. Katzner, S., Busse, L., and Carandini, M. (2011). GABAA inhibition controls response gain in visual cortex. J. Neurosci. *31*, 5931–5941.
40. Morrone, M.C., and Burr, D.C. (1986). Evidence for the existence and development of visual inhibition in humans. Nature *321*, 235–237.
41. Morrone, M.C., Burr, D.C., and Speed, H.D. (1987). Cross-orientation inhibition in cat is GABA mediated. Exp. Brain Res. *67*, 635–644.
42. Boynton, G.M., Demb, J.B., Glover, G.H., and Heeger, D.J. (1999). Neuronal basis of contrast discrimination. Vision Res. *39*, 257–269.
43. Ling, S., and Blake, R. (2012). Normalization regulates competition for visual awareness. Neuron *75*, 531–540.
44. Ding, J., and Sperling, G. (2006). A gain-control theory of binocular combination. Proc. Natl. Acad. Sci. USA *103*, 1141–1146.
45. Zhou, J., Clavagnier, S., and Hess, R.F. (2013). Short-term monocular deprivation strengthens the patched eye's contribution to binocular combination. J. Vis. *13*, 12.