Homer1a Is Required for Establishment of Contralateral Bias and Maintenance of Ocular Dominance in Mouse Visual Cortex

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It is well established across many species that neurons in the primary visual cortex (V1) display preference for visual input from one eye or the other, which is termed ocular dominance (OD). In rodents, V1 neurons exhibit a strong bias toward the contralateral eye. Molecular mechanisms of how OD is established and later maintained by plastic changes are largely unknown. Here we report a novel role of an activity-dependent immediate early gene Homer1a (H1a) in these processes. Using both sexes of H1a knock-out (KO) mice, we found that there is basal reduction in the OD index of V1 neurons measured using intrinsic signal imaging. This was because of a reduction in the strength of inputs from the contralateral eye, which is normally dominant in mice. The abnormal basal OD index was not dependent on visual experience and is driven by postnatal expression of H1a. Despite this, H1a KOs still exhibited normal shifts in OD index following a short-term (2–3 d) monocular deprivation (MD) of the contralateral eye with lid suture. However, unlike wild-type counterparts, H1a KOs continued to shift OD index with a longer duration (5–6 d) of MD. The same phenotype was recapitulated in a mouse model that has reduced Homer1 binding to metabotropic glutamate receptor 5 (mGluR5). Our results suggest a novel role of H1a and its interaction with mGluR5 in strengthening contralateral eye inputs during postnatal development to establish normal contralateral bias in mouse V1 without much impact on OD shift with brief MD.

Key words: Homer1a; immediate early gene; monocular deprivation; ocular dominance; visual cortex

Significance Statement
Visual cortical neurons display varying degree of responsiveness to visual stimuli through each eye, which determines their ocular dominance (OD). Molecular mechanisms responsible for establishing normal OD are largely unknown. Development of OD has been shown to be largely independent of visual experience, but guided by molecular cues and spontaneous activity. We found that activity-dependent immediate early gene H1a is critical for establishing normal OD in V1 of mice, which show contralateral eye dominance. Despite the weaker contralateral bias, H1a KOs undergo largely normal OD plasticity. The basic phenotype of H1a KO was recapitulated by mGluR5 mutation that severely reduces H1a interaction. Our results suggest a novel role of mGluR5-H1a interaction in strengthening contralateral eye inputs to V1 during postnatal development.
stages. Monocular deprivation (MD) first produces depression of the deprived eye response (2–3 d MD) through homeosynaptic LTD mechanisms (Dudek and Bear, 1992; Kirkwood et al., 1993; Rittenhouse et al., 1999) followed by a delayed component (5–6 d MD), which resembles homeostatic mechanisms, leading to strengthening of open-eye responses (Sawtell et al., 2003; Frenkel and Bear, 2004; Mrsic-Flogel et al., 2007; Ranson et al., 2012).

There is strong evidence that weakening of the deprived eye response is because of NMDAR-dependent LTD mechanisms (Rittenhouse et al., 1999; Heynen et al., 2003; Sawtell et al., 2003; Crozier et al., 2007), whereas there are a couple of alternatives proposed as the homeostatic plasticity mechanisms triggered during the later phase of OD plasticity (5–6 d MD). One mechanism proposed is synaptic scaling, which induces global cell-wide changes, hence can explain the parallel potentiation of both eye responses during the second phase of OD plasticity (Kaneko et al., 2008; Ranson et al., 2012). A second mechanism proposed is NMDAR-dependent metaplasticity, where loss of inputs coming from the deprived eye reduces the synaptic modification threshold to allow inputs from the open eye to potentiate following prolonged MD (Sawtell et al., 2003; Frenkel and Bear, 2004; Chen and Bear, 2007; Cho et al., 2009). The latter mechanism allows for input-specific changes and can explain potentiation of previously weaker inputs, as would happen when the dominant contralateral eye is sutured.

Homer1a (H1a) is an immediate early gene expressed with increase in neuronal activity (Brakeman et al., 1997; Hu et al., 2010), and its expression is increased in V1 upon light exposure following a period of dark adaptation (Brakeman et al., 1997). Hence H1a is well posed to respond to changes in visual experience. In addition, H1a is involved in homeostatic synaptic scaling observed in neuronal cultures upon chronic increase in activity (Hu et al., 2010) suggesting a role in homeostatic control of excitatory synaptic transmission. In this study, we aimed to study whether activity-dependent H1a expression is required for any of the processes mediating OD plasticity. Our initial hypothesis was that it would be involved in the homeostatic maintenance phase of OD with prolonged MD. Using optical imaging of intrinsic signals in V1, we report two novel mechanisms of H1a in OD plasticity: (1) H1a expression is required for the establishment of normal contralateral bias by strengthening contralateral eye inputs during postnatal development, which is independent of visual experience, and (2) H1a is not necessary for OD shift with short-term MD (2–3 d) but is involved in the later phase of OD plasticity (5–6 d MD).

Materials and Methods

Animals. Male and female mice were reared in a 12 h light/dark cycle. The knock-out for H1a (H1aKO), knock-in on the Fl128R amino acid in the C-terminus of metabotropic glutamate receptor 5 (mGlur5; FRKI), and floxed-Homer1 (Homer1fl/fl) line were obtained from Dr. Paul Worley (Johns Hopkins School of Medicine, Baltimore). Wild-type strains for H1aKO and FRKI were generated by breeding mutant mice with C57BL/6 (The Jackson Laboratory) mice, yielding H1aWT and FRWT, respectively. To create a conditional knock-out for H1a with the normal long form of Homer1, we created a H1aKOfloxed line (H1b/−/−; H1afl/fl) by crossing Homer1fl/fl mice with H1aKO mice. H1aWTfloxed mice (H1b/−/−; H1afl/fl) were generated by breeding Homer1fl/fl mice with H1aWT mice. All the animals were handled according to protocols approved by the Institutional Animal Care and Use Committee and guidelines provided by the Animal Care Act and National Institutes of Health.

Visual deprivation by dark rearing. Pregnant females and new born pups were dark reared (DR) in a dark room and were cared for with infrared vision goggles using dim infrared light. DR animals (see Fig. 3) were anesthetized in the dark room and brought to the imaging setup in a light tight box to minimize exposure to light.

MD by eye lid suture. Animals were monocularly deprived after each control imaging session by performing a monocular lid suture. During the procedure, animals were maintained at a deep anesthetic level using 1.5–2% isoflurane in oxygen (flow rate 1.0 L/min). Lid suturing was performed on the eye contralateral to the imaged V1. The upper and lower lids were slightly trimmed and then sutured together (Prolene P-6; Ethicon catalog #8648G). Animals recovered on a heating pad and then were returned to the animal colony. Each animal was housed individually until the next imaging session.

Bola virus injection in newborn pups. The home cage, containing pups and their mother, was brought to the injection setup. Pups (P0–P2) were anesthetized by placing them between a wet paper towel surrounded by ice for 5 min (Phifer and Terry, 1986). Under a dissection scope, V1 was located and viral injection was performed using an injection pump at 100 nl/s. The left hemisphere of each pup was injected with virus (200 nl). Pups recovered at 37°C before being returned to their home cage. H1aKOfloxed or H1aWTfloxed (Worley laboratory, Johns Hopkins School of Medicine) were injected in V1 with either a Cre-expressing virus (AAV9.CaMKII.HI.eGFP.Cre.WPRE.SV40) to knock-out the floxed Homer1 hemi-gene or with a control enhanced GFP virus (AAV9. CaMKII.4.eGFP.WPRE.CAG.BG) to provide a control group.

Optical imaging of intrinsic signals. Mice were brought to the imaging setup in a fresh cage and anesthetized with 3% isoflurane in O2 (flow rate: 1.0 L/min). The animals were head-fixed using a stereotaxic apparatus (Kopf Instruments) and maintained with constant level of isoflurane (~0.75%) in O2 (flow rate: 1.0 L/min) with single injection of chlorprothixene hydrochloride (Sigma-Aldrich, C1671; 2 mg/kg in saline). Heart rate was monitored and recorded during the imaging session using an EKG instrument (EKG, Harald Stauss Scientific). Temperature was maintained at 37°C with a heating pad. The imaging method developed in the Stryker laboratory (Kalatsky and Stryker, 2003; Gang et al., 2005) was used to measure the ocular dominance index in juvenile mice (P25–P35). A visual stimulus consisting of a horizontal bar moving in a vertical direction (upward and downward) was displayed in the binocular visual field (~5°–15° azimuth) to elicit responses in the binocular zone of V1. Vasculature was visualized by illuminating the surface of the brain with 555 nm light. Elicited responses were measured as changes in the reflectance of 610 nm light and were imaged transcranially with a Dalsa CCD camera through a coverslip fixed with 3% agarose. For each eye, cortical activity elicited at the stimulus frequency was calculated by Fourier analysis and presented as 3R/3R (reflectance of 610 nm light). The ocular dominance index was calculated as an average of (Contra-Ipsi)/ (Contra+Ipsi) from each pixel in a region-of-interest, which was manually selected on the basis of raw signal from ipsilateral eye responses with a threshold of at least 40% of the maximum signal intensity.

Confirmation of viral transfection by immunohistochemistry. Animals were deeply anesthetized with isoflurane after the final imaging session and were then transcardially perfused with 10 ml of 0.1 M PBS followed by 10 ml of 10% formalin in 0.1 M PBS. Brains were then harvested and fixed overnight in 10% formalin. V1 was isolated and 40 μm thick slices were collected using a vibratome (Ted Pella). Free-floating sections were rinsed with PBS and permeabilized with 2% Triton X-100 buffered in PBS solution. Following another wash, the slices were incubated in blocking buffer (10% normal donkey serum, 0.2% Triton X-100, 4% bovine serum albumin). Primary antibody treatment for NeuN (1:100 in blocking buffer; Millipore, catalog# MBA377) was performed for 2 d at 4°C. Afterward, slices were washed with PBS twice and treated with secondary antibody (Rabbit anti-mouse AlexaFluor 633; ThermoFisher Scientific). Slices were then washed, mounted on glass slides, and dried at room temperature for 20 min. Coverslips were affixed using mounting media (Prolong gold antifade, Invitrogen) and sealed with nail polish. Slices were later imaged for NeuN (633) and Cre (GFP) expression with an LSM 510 confocal microscope.

Experimental design and statistical analysis. Experiments were designed to determine whether changes in ocular dominance associated with experimental manipulation (e.g., MD or DR) and/or genotype. All data are displayed as mean ± standard error of mean (SEM). ANOVAs, two-way ANOVAs, and unpaired t tests
were performed using GraphPad Prism, as mentioned in each figure legend. Newman–Keuls multiple-comparison post hoc test was used following ANOVA to determine statistically significant difference between multiple groups as noted in each figure legend. Raw data are available on request.

**Results**

**H1aKO exhibit abnormal contralateral bias and fails to maintain homeostatic OD plasticity**

The role of H1a in OD plasticity was assessed by imaging of intrinsic signals produced in V1 by presentation of visual stimuli to the contralateral eye compared with that of the ipsilateral eye (ODI), which is basically a measure of response ratio between contralateral eye (contra) and ipsilateral eye (ipsi) responses in V1. Several mechanisms triggered by prolonged deprivation of visually-driven eye inputs to V1.

In wild-type mice, 2–3 d MD significantly depressed deprived eye (contra) responses leading to a reduction in the contra eye responses (Fig. 3). In wild-type mice, 2–3 d MD did not produce significant changes in the open-eye responses (Fig. 3B). However, a longer duration MD (5–6 d MD) led to strengthening of the open-eye (ipsi) responses along with a slight increase in deprived eye responses (Fig. 3B). This led to a maintenance of ODI with longer MD to a similar level as that observed with shorter MD (Fig. 3A).

To determine whether H1a is involved in ocular dominance plasticity (ODP), we next performed varying durations of MD by suturing the contralateral eye (Fig. 3). In wild-type mice, 2–3 d MD significantly depressed deprived eye (contra) responses leading to a shift in ODI toward the open eye (ipsi) (Fig. 3A). As reported earlier (Frenkel and Bear, 2004; Sato and Stryker, 2008; Ranson et al., 2012), this short duration MD (2–3 d MD) did not produce significant changes in the open-eye responses (Fig. 3B). However, a longer duration MD (5–6 d MD) led to strengthening of the open-eye (ipsi) responses along with a slight increase in deprived eye responses (Fig. 3B). This led to a maintenance of ODI with longer MD to a similar level as that observed with shorter MD (Fig. 3A). Such maintenance of ODI with longer MD has been attributed to homeostatic plasticity mechanisms triggered by prolonged deprivation of visually-driven activity (Ranson et al., 2012).

Despite the reduced contralateral bias under normal conditions, upon 2–3 d MD H1aKO mice were able to produce normal
Depression of deprived-eye responses without affecting open-eye responses (Fig. 3D) resulting in a normal shift of ODI toward the open eye (Fig. 3C). However, ODI further shifted toward the open eye (ipsi) with 5–6 d MD (Fig. 3C). We observed normal open-eye potentiation during this phase of MD in H1a knockouts (KOs; Fig. 3D), which suggests that H1a is not involved in this process. Our results indicated that H1a is not necessary for OD plasticity, but is required for the maintenance of ODI during longer periods of MD. In addition, we found a novel role of H1a in setting up normal contralateral bias in rodent V1.

H1a is necessary for postnatal establishment of contralateral bias

Postnatal development of visual cortex involves refinement of connections that confers the cells with ocular selectivity. This phase occurs before eye opening in mice (Rakic, 1976; Li et al., 2008; Rochefort et al., 2011). However, visual experience after eye opening is necessary for maturation of individual eye responses in mammals including mice (Hubel and Wiesel, 1963; Wiesel and Hubel, 1974; Smith and Trachtenberg, 2007). Based on our observation of a lower basal ODI in H1aKO, we examined whether this is because of lacking visual experience-dependent changes. To do this, we examined whether normal visual experience is needed to establish ODI in H1aWT and H1aKO mice by dark rearing them from birth (Fig. 4A). ODI value in both H1aWT and H1aKO mice after dark rearing were comparable to their respective age-matched normal reared groups (Fig. 4B,D), suggesting that visual experience is not necessary to establish normal ODI values in either genotype. However, responses from individual eyes were significantly weaker as compared with normal reared animals in both genotypes (Fig. 4C,E). Our results suggest that basal ODI measured in critical period mice is setup independent of visual experience. Based on this, we conclude that the lower basal ODI values seen in H1aKO are not because of abnormal responses to visual experience during development but are because of a novel role of H1a in establishing contralateral eye input dominance in a visual experience-independent manner.

H1aKO is a constitutive KO; hence we cannot rule out abnormalities in prenatal development that could have contributed to lower basal ODI. Prenatal development of visual cortex in mice involve genetic mechanisms that lay the chemo-

Figure 3. H1aKO mice show normal ODP with short-term MD, but fail to maintain ODI with longer-term MD. Data shown as mean ± SEM. Response magnitude is of the order ×10⁻². Statistics, ANOVA with Newman–Keuls multiple-comparison test. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. A. Left, Average ODI data measure in H1aWT with 2–3 d MD and 5–6 d MD. ODI: Ctrl = 0.34 ± 0.02, 2–3 d MD = 0.22 ± 0.03, 5–6 d MD = 0.19 ± 0.04, ANOVA, F(2,41) = 9.401, p = 0.0004; Newman–Keuls multiple-comparison test. Right, Example signals for each eye stimulation for corresponding MD and Ctrl groups. Scale Bar, 1 mm. Number of animals, n = 22, 2–3 d MD = 11, 5–6 d MD = 11. B. Contralateral and ipsilateral eye response magnitude measured in H1aWT mice during MD paradigms. Contra: Ctrl = 2.62 ± 0.10, 2–3 d MD = 2.14 ± 0.17, 5–6 d MD = 2.48 ± 0.12, ANOVA, F(2,41) = 3.498, p = 0.0396; Newman–Keuls multiple-comparison test; Ipsi: Ctrl = 1.28 ± 0.05, 2–3 d MD = 1.30 ± 0.12, 5–6 d MD = 1.65 ± 0.12, ANOVA, F(2,41) = 5.194, p = 0.0098; Newman–Keuls multiple-comparison test. n, same as in A. C. Left, Average ODI data measure in H1aKO with 2–3 d MD and 5–6 d MD. Right, Example signals for each eye stimulation for corresponding MD and Ctrl groups. ODI: Ctrl = 0.14 ± 0.02, 2–3 d MD = 0.01 ± 0.03, 5–6 d MD = −0.08 ± 0.04, ANOVA, F(2,41) = 18.200, p < 0.0001; Newman–Keuls multiple-comparison test. Right, Example signals for each eye stimulation for corresponding MD and Ctrl groups. Scale Bar, 1 mm. Number of animals, n = 25, 2–3 d MD = 16, 5–6 d MD = 9. D. Contralateral and ipsilateral eye response magnitude in H1aKO mice. Contra: Ctrl = 1.65 ± 0.09, 2–3 d MD = 1.28 ± 0.11, 5–6 d MD = 1.49 ± 0.10, ANOVA, F(2,41) = 3.479, p = 0.0390; Newman–Keuls multiple-comparison test. Ipsi: Ctrl = 1.18 ± 0.06, 2–3 d MD = 1.21 ± 0.09, 5–6 d MD = 1.65 ± 0.12, ANOVA, F(2,41) = 7.241, p = 0.0018; Newman–Keuls multiple-comparison test. n, same as in C.
Developmental establishment of contralateral bias is not visual experience-dependent in both H1aWT and H1aKO. Data shown as mean ± SEM. Response magnitude is of the order $10^{-4}$. Statistics. Unpaired two-tailed Student’s t test. 

**p < 0.05, ***p < 0.001, ****p < 0.0001,  

| Condition | OD1 | OD2 | H1aWT | ns | Contra | ipsi | Scale Bar, 1 mm. Number of animals, n: NR = 22 DR = 7.  

**Contra** | ipsi | Scale Bar, 1 mm. Number of animals, n: NR = 22 DR = 7.  

| Condition | OD1 | OD2 | H1aWT | ns | Contra | ipsi | Scale Bar, 1 mm. Number of animals, n: NR = 22 DR = 7.  

**Contra** | ipsi | Scale Bar, 1 mm. Number of animals, n: NR = 22 DR = 7.  

**H1aKO** | H1aWTflox mice (H1b/cfl/fl;H1afl/fl) with H1aKO mice, which produced H1aWTflox mice (H1b/cfl/fl;H1afl/fl) with H1aWT, without any viral injections these mice are wild-type for both H1b/c and H1a (H1b/c+/−; H1a+/−). Without any viral injections these mice are wild-type for both H1b/c and H1a (H1b/c+/−; H1a+/−), and with Cre-GFP injection they produce neurons which are heterozygous for both H1b/c and H1a (H1b/c+/−; H1a+/−). As summarized in Figure 6, by comparing the four groups (H1b/c+/−; H1a+/−; H1b/c−/−; H1a+/−; H1b/c+/−; H1a+/−), we can compare dose-dependent effects of H1b/c and H1a expression. ODI measurement was done during the critical period of OD plasticity (P28–P35; Fig. 6). All the animals were confirmed for expression of virus after the imaging session (Fig. 5C,D). The transfection efficiency in groups receiving Cre-GFP virus (H1b/c+/−; H1a+/− and H1b/c−/−; H1a+/−) was ~90%.  

**Conditional H1a KO neurons (H1b/c+/−; H1a+/−)** had significantly lower contralateral bias than the Homer1 wild-type group (H1b/c+/−; H1a+/−; Fig. 6A). However, heterozygous H1a controls (H1b/c+/−; H1a+/− and H1b/c+/−; H1a+/−) were not significantly different from either of the groups, which suggests that there might be H1a gene dose-dependent regulation of ODI during postnatal development. Although there was a trend of a decrease in contralateral eye responses and a slight increase in ipsilateral eye responses in the H1b/c+/−; H1a+/− group, this did not reach statistical significance when compared with other groups (Fig. 6B). These observations support the premise that H1a expression during postnatal development is required to establish normal contralateral bias in V1.
Furthermore, long-term MD (5–6 d MD) produced significantly greater decrease in ODI than the wild-type animals similar to what we observed in H1aKO (two-way ANOVA for ODI between FRWT versus FRKI shows statistically significant interaction: \( p = 0.0471, F_{(1,12)} = 4.892; \) Fig. 7). Our results suggest that mGluR5 interaction with Homer1 is required for establishing basal ODI and for maintenance of OD during longer durations of MD (5–6 d MD). Although we cannot exclude the possibility that FRKI phenotype is because of reduced binding of mGluR5 to long forms of Homer1, our observation that FRKI phenocopies H1aKO can be explained most parsimoniously by the loss of mGluR5–H1a interaction. Furthermore, long forms of Homer1 are expressed in greater abundance compared with its splice variant H1a, hence reduced affinity of mGluR5 to these two splice variants is expected to more severely affect the formation of mGluR5–H1a complexes.

Discussion
The main finding of this study is that H1a and its interaction with mGluR5 are required for establishing the normal contralateral bias in V1 and maintenance of OD following longer periods of MD. Even with the lower basal ODI, H1aKO displayed OD shifts with short-term MD, which suggests that the initial phase of MD, which is mainly driven by weakening of the closed-eye inputs, is not dependent on H1a expression. Moreover, we found evidence that H1a and mGluR5 interaction is critical for establishing the basal ODI and for preventing a further decrease in ODI during longer-term MD.

H1a is not necessary for OD plasticity with short-term MD, but needed for preventing a further shift in ODI with long-term MD
Short-term MD (2–3 d MD) predominantly drives weakening of the closed-eye inputs via NMDAR-dependent LTD mechanisms (Rittenhouse et al., 1999; Heynen et al., 2003; Sawtell et al., 2003; Crozier et al., 2007). Longer duration MD (5–6 d MD) has a delayed additional component that is thought to be produced by homeostatic plasticity that involves potentiation of open-eye inputs (Sawtell et al., 2003; Frenkel and Bear, 2004; Chen and Bear, 2007; Kaneko et al., 2008; Cho et al., 2009; Ranson et al., 2012). Recently it was reported that global synaptic scaling mechanisms through glial-derived tumor necrosis factor (TNFa; Kaneko et al.,

Figure 5. Generation of H1a conditional KO neurons in V1. A, Experimental design for bolus injection of AAV virus at birth and ODI measurement during critical age for ODP. B, Genetic design to produce H1a conditional KO neurons in cortex. Inj, Injection. For virus information see methods. C, Example slices showing transfection levels of virus in V1 L2/3 in all the three conditions. NeuN (red), Neuronal marker; GFP (green), marker for viral infection. D, Quantification for viral transfection efficiency as percentage of GFP-expressing cells per NeuN-expressing neurons.
2008) are required for this later phase of ODP. TNFα has been shown to be specifically involved in homeostatic plasticity and is not necessary for Hebbian forms of plasticity (Beattie et al., 2002; Kaneko et al., 2008; Steinmetz and Turrigiano, 2010; Pribiag and Steinmetz, 2010). Steinmetz and Turrigiano, 2010; Pribiag and Steinmetz, 2010) and not necessary for Hebbian forms of plasticity (Beattie et al., 2002; Heynen et al., 2003). However, we found that H1a KOs display a further reduction in ODI upon longer duration of MD (5–6 d; Fig. 3). In wild-types, ODI does not shift further because of a delayed potentiation of both the deprived eye and the open-eye inputs (Fig. 3). The delayed open-eye potentiation was still intact in H1a KOs suggesting that H1a is not involved in this process. The larger reduction in ODI seen with longer-term MD (5–6 d; Fig. 3) was recapitulated in mGluR5 knock-in mice that have a delayed potentiation of both the deprived eye and the open-eye inputs (Fig. 3). This suggests that H1α interaction with mGluR5 plays a role in preventing a further reduction in ODI during the later phase of MD.

**Development of OD**

Development of OD of V1 neurons happens before eye opening in mice and kittens. Establishment of OD is dependent on retinal spontaneous activity rather than visual experience (Hubel and Wiesel, 1963; Stryker and Harris, 1986; Crair et al., 1998). Block-
ode of spontaneous retinal activity after eye opening prevents the normal development of thalamocortical arborization in V1 layer 4 (Antonini and Stryker, 1993). In addition, correlated spontaneous activity in the visual thalamus (LGNd) is sufficient to produce ocular dominance columns in ferret V1 (Weliky and Katz, 1999; Chiu and Weliky, 2001). Consistent with these studies, we found that normal contralateral bias is established even when mice are dark reared from birth with no visual experience (Fig. 4B). However, molecular mechanisms underlying the normal establishment of OD are not well understood. We found that establishment of contralateral bias is severely impacted in H1aKO mice, which persisted even when H1aKO are raised in the dark from birth (Fig. 4D). This was because of abnormally weak contralateral responses in V1. Ipsilateral eye responses were similar to what is observed in WTs. Furthermore, we demonstrated that postnatal expression of H1a is important for this contralateral bias, because inducing conditional KO of H1a postnatally recapitulated the lower ODI (Fig. 6A). This suggests that spontaneous activity in the absence of vision, such as retinal waves or spontaneous LGN and/or cortical activity, may be sufficient to trigger H1a activation to support the development of contralateral bias in V1. The exact mechanism in which H1a regulates the strength of contralateral eye inputs will require further studies, but we demonstrated that its interaction with mGluR5 is critical for this process using mice carrying mutations on the mGluR5 that lack H1a binding (FRKI; Fig. 7). Although the role of H1a in homeostatic scaling down of synaptic strength has been shown in neuronal cultures (Hu et al., 2010), its role in strengthening inputs has not been reported. Furthermore, our results would suggest that H1a rather selectively works on contralateral eye inputs to establish the normal contralateral bias. The exact mechanism as to how H1a can achieve input-specific control of contralateral eye inputs would require further investigation. On the surface, our results differ from a proposed role of H1a in global homeostatic downregulation of synaptic strength as reported in cultured neurons (Hu et al., 2010), which may be because of differences in preparation. One potential explanation that could reconcile this apparent contradiction is that mGluR5–H1a interaction enables plasticity, but does not determine the polarity of synaptic plasticity, and whether it results in global or specific LTD/LTP. In preparation. One potential explanation that could reconcile this apparent contradiction is that mGluR5–H1a interaction enables plasticity, but does not determine the polarity of synaptic plasticity, and whether it results in global or specific LTD/LTP.
input-specific plasticity may be determined by the nature of neu-
ral activity received via distinct inputs.

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