Brief Communications

The Role of GluA1 in Ocular Dominance Plasticity in the Mouse Visual Cortex

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Ocular dominance plasticity is a widely studied model of experience-dependent cortical plasticity. It has been shown that potentiation of open eye responses resulting from monocular deprivation relies on a homeostatic response to loss of input from the closed eye, but the mechanisms by which this occurs are not fully understood. The role of GluA1 in the homeostatic component of ocular dominance (OD) plasticity has not so far been tested. In this study, we tested the idea that the GluA1 subunit of the AMPA receptor is necessary for open eye potentiation. We found that open eye potentiation did not occur in *GluA1 knock-out* (*GluA1*$^{-/-}$) mice but did occur in wild-type littermates when monocular deprivation was imposed during the critical period. We also found that depression of the closed eye response that normally occurs in the monocular as well as binocular zone is delayed, but only in the monocular zone in *GluA1*$^{-/-}$ mice and only in a background strain we have previously shown lacks synaptic scaling (C57BL/6OlaHsd). In adult mice, we found that OD plasticity and facilitation of OD plasticity by prior monocular experience were both present in *GluA1*$^{-/-}$ mice, suggesting that the GluA1-dependent mechanisms only operate during the critical period.

Introduction

Ocular dominance (OD) plasticity in the visual cortex is induced by closing one eye during the critical period of development and leads to weakening of the closed eye responses and strengthening of the open eye responses (Wiesel and Hubel, 1963; Sato and Stryker, 2008). Strengthening of the open eye response is thought to be a homeostatic reaction to a decrease in activity following deprivation and to depend on synaptic scaling, since antagonizing or knocking out factors that disrupt scaling also disrupt open eye potentiation (Kaneko et al., 2008; Ranson et al., 2012). Studies have shown that phosphorylation of the GluA1 subunit of the AMPA receptor (previously known as GluR1) is important for homeostatic plasticity following monocular deprivation in the visual cortex (Goel et al., 2011; He et al., 2011). However, the role of GluA1 in the homeostatic component of OD plasticity has not previously been tested directly. We therefore studied the role of GluA1 in OD plasticity by monocularly depriving *GluA1 knock-out* mice and their wild-type littermates during the critical period and measuring cortical responses to visual stimulation using intrinsic signal imaging (ISI). We tested the role of GluA1 in two substrains of C57BL/6 mice; the C57BL/6J strain that exhibits synaptic scaling and C57BL/6OlaHsd that does not. As adult plasticity in the visual cortex appears to depend on different mechanisms to critical period plasticity (Ranson et al., 2012), we also studied plasticity in adult mice.

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Materials and Methods

Subjects. Animal procedures were performed in accordance with the UK Animals (Scientific Procedures) Act 1986. *GluA1*$^{-/-}$*OlaHsd* were obtained from Rolf Sprengel (Max Planck Institute, Germany) via Nick Rawlins' lab (Oxford, UK) and outbred into a C57BL/6OlaHsd background (Harlan). *GluA1*$^{-/-}$*6J* is a line generated from *GluA1*$^{-/-}$*OlaHsd* by backcrossing into a C57BL/6J (The Jackson Laboratory) background for nine generations.

Visual deprivation. Mice of either sex were reared on a 12 h light/12 h dark cycle. For *in vivo* experiments, mice were monocularly deprived by eyelid suture under isoflurane anesthesia (2% in O_2, 0.6 l/min). For critical period studies, monocular deprivation (MD) began at P26–P27 and lasted for 3 or 5–6 d. In adult studies, initial MDs began at P90–P120 and lasted for 6–7 d. This was followed by reopening of the eye and 4 weeks of recovery with normal visual experience. Animals underwent a further 3 d of MD to assess facilitation of plasticity by prior experience. The integrity of the deprivation was checked daily and immediately before ISI. The experiment was discontinued if the deprivation was impaired.

In vivo *intrinsic signal imaging.* Acute ISI was performed in the primary visual cortex contralateral to the deprived eye (Fig. 1*A*,*B*). The visual cortex was imaged transcranially using 0.8–1% isoflurane in O_2 at 0.3 l/min, supplemented with 25 μg of chlorprothixene as previously described, to measure OD (Hofer et al., 2006; Kaneko et al., 2008). For quantification of OD, visual responses were elicited using a 0.03 cycles/deg square-wave grating drifting at 2 cycles per second presented in the binocular or monocular visual field, with the stimulated eye determined by computer controlled eye shutters. Ocular dominance index (ODI) was calculated by the formula $(C - I)/(C + I)$ where C and I are the contralateral and ipsilateral response magnitudes, respectively (Fig. 1*B*). Response magnitudes are presented as $\Delta R/R$ values where R is light reflected.

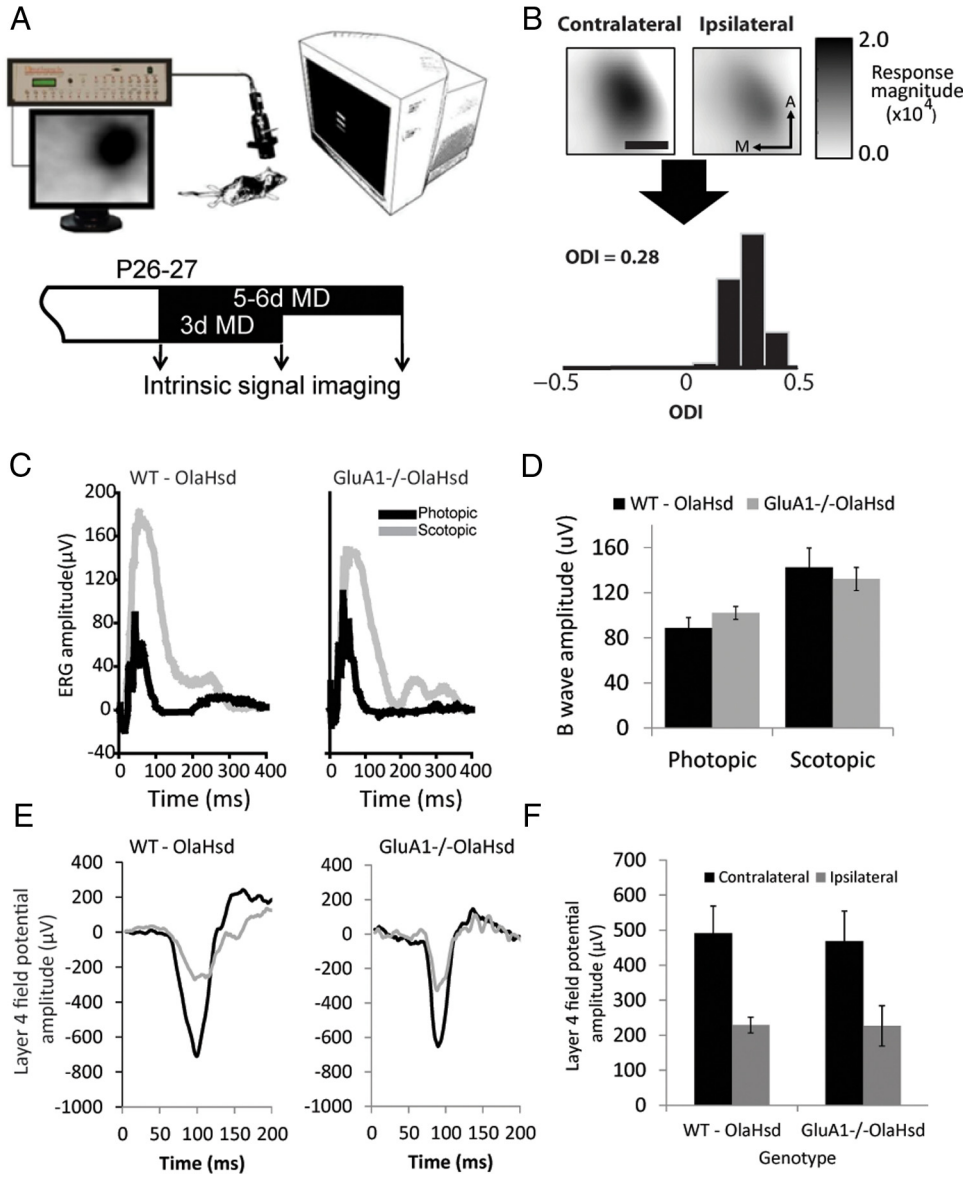

Figure 1. ISI methodology and transmission of visual information in *GluA1*$^{-/-}$ mice (OlaHsd background). ***A***, Top, Schematic of the ISI setup. Below, The deprivation and imaging timeline. ***B***, Representative activity maps of WT and *GluA1*$^{-/-}$*OlaHsd* mice for monocular stimulation of the contralateral and ipsilateral eye. Scale bar, 500 μm. ***C***, ERG waveforms under photopic (black) and scotopic (gray) conditions. ***D***, B-wave amplitude under photopic and scotopic conditions (in μV, mean $\pm$ SEM). There was no effect of genotype (photopic: $t = 0.12$, $p = 0.27$; scoptopic: $t = 0.53$, $p = 0.61$). ***E***, Example VEP traces from WT and *GluA1*$^{-/-}$*OlaHsd* mice, showing contralateral (black) and ipsilateral (gray) responses. ***F***, Average maximum field potential amplitudes of WT mice and *GluA1*$^{-/-}$*OlaHsd* littermates. There was no effect of genotype (contralateral eye: $t = 0.19$, $p = 0.84$; ipsilateral eye: $t = 0.04$, $p = 0.97$).

Visual-evoked potentials. Visual-evoked potentials (VEPs) were recorded under the same anesthetic conditions as ISI using 0.1 MΩ impedance Parylene-C insulated tungsten microelectrodes (Intracel). Signals were acquired at 25 kHz, bandpass filtered (0.3–300 Hz), and amplified (x5–10k). The recording electrode was gradually lowered 50 μm at a time while the animal was being visually stimulated until a short (~60 ms) latency maximally negative-going field potential was observed—invariably this was at a depth of 400–450 μm, which corresponds to layer 4 (Sawtell et al., 2003). Stimulus triggered recordings were then made of VEPs in response to a contrast reversing grating presented to the binocular visual field of each eye individually. Each eye was stimulated 40–80 times, divided into alternating eye blocks of 20 stimulations per eye. VEP amplitude was measured at the trough of the layer 4 field potential.

Electroretinograms. Electroretinograms (ERGs) were recorded from anesthetized mice under photopic and scotopic conditions using previously described methods (Pearson et al., 2012).

Statistics. ANOVA statistics were used to make initial comparisons between groups of animals in each case followed by *post hoc t* tests. The results of the *post hoc* tests are quoted in the text. In some experiments, measurements were made from the same animals across deprivation conditions; in these cases, paired *t* tests were used.

Results

GluA1 is required for normal sensory transmission in cortical layers 2/3

GluA1 is an important subunit for excitatory transmission under normal conditions. Therefore, we wanted to determine whether sensory responses were normal in the *GluA1 knock-out* mice throughout the ascending visual pathway. We made electrical recordings from the retina (ERGs) and visually evoked potential recordings from visual cortical layer 4 (VEPs) to compare activity in *GluA1*$^{-/-}$*OlaHsd* and WT littermate mice. There were no differences in ERG (Fig. 1*C*,*D*) or cortical VEP amplitude (Fig. 1*E*,*F*) between the two genotypes, suggesting that sensory transmission from the photoreceptor to layer 4 of the cortex was nor-

mal or compensated for in the knock-out. However, using ISI of cortical responses evoked by visual stimuli, we observed that response magnitudes were on average ~30% smaller in control *GluA1*$^{-/-}$*OlaHsd* than in their WT littermates (Fig. 2*A*,*B*; response magnitudes are of the order $\times 10^{-4}$ ± SEM; control contralateral monocular responses, WT: 1.87 ± 0.16, *GluA1*$^{-/-}$*OlaHsd*: 1.27 ± 0.13; $p < 0.05$; $t = 2.82$). This suggests that GluA1 is important for sensory transmission within layer 2/3 as the intrinsic signal is dominated by activity in the superficial cortical layers. The ODI was not affected by the smaller cortical ISI responses and was identical between genotypes (Fig. 2*D*; WT: 0.28 ± 0.15, *GluA1*$^{-/-}$*OlaHsd*: 0.28 ± 0.35) and within the normal range for undeprived mice (Ranson et al., 2012).

Response depression is delayed in the monocular zone in *GluA1-OlaHsd*$^{-/-}$ mice

A 3 d period of MD during the postnatal sensitive period results in a loss of cortical responsiveness to the closed eye. We tested the dependence of this process on GluA1 by measuring visually evoked responses in mice lacking GluA1 and comparing them to their WT littermates. We studied this process in mice on the C57BL/6OlaHsd background, which lacks synaptic up-scaling (Ranson et al., 2012), to judge the effect of GluA1 deletion in relative isolation from the homeostatic compensation of up-scaling.

Following 3 d MD, closed eye response magnitudes in the binocular zone (BZ) were depressed to a similar extent in *GluA1*$^{-/-}$*OlaHsd* and WT-OlaHsd mice (Fig. 2*A*). However, in the monocular zone (MZ), closed eye depression only occurred in WT mice (Fig. 2*C*; MZ response: WT: shifted from 1.87 ± 0.16 to 1.23 ± 0.08, $p < 0.01$, $t = 3.70$; *GluA1*$^{-/-}$*OlaHsd*: did not shift 1.27 ± 0.13 and 1.24 ± 0.17, $p = 0.91$, $t = 0.11$).

After 5–6 d MD, closed eye response magnitudes decreased significantly in the MZ for both genotypes (*GluA1*$^{-/-}$*OlaHsd*; shifted from 1.24 ± 0.17 to 0.44 ± 0.07, $p < 0.005$, $t = 3.83$, WT-OlaHsd; 1.23 ± 0.10 to 0.835 ± 0.13, $p < 0.05$, $t = 2.21$). In the BZ, closed eye responses decreased further after 5–6 d MD compared with 3 d MD in the *GluA1*$^{-/-}$*OlaHsd* (shifted from 0.74 ± 0.08 to 0.28 ± 0.05, $p < 0.001$, $t = 4.73$) but not in the WT-OlaHsd mice (0.87 ± 0.07 and 0.72 ± 0.05 $p = 0.22$, $t = 1.25$). Open eye responses were not significantly different at the 3 or 5–6 d time points compared with un-deprived controls for either genotype ($\alpha = 0.05$) and no potentiation was seen, even in the WT-OlaHsd mice, as has been reported previously (Ranson et al., 2012).

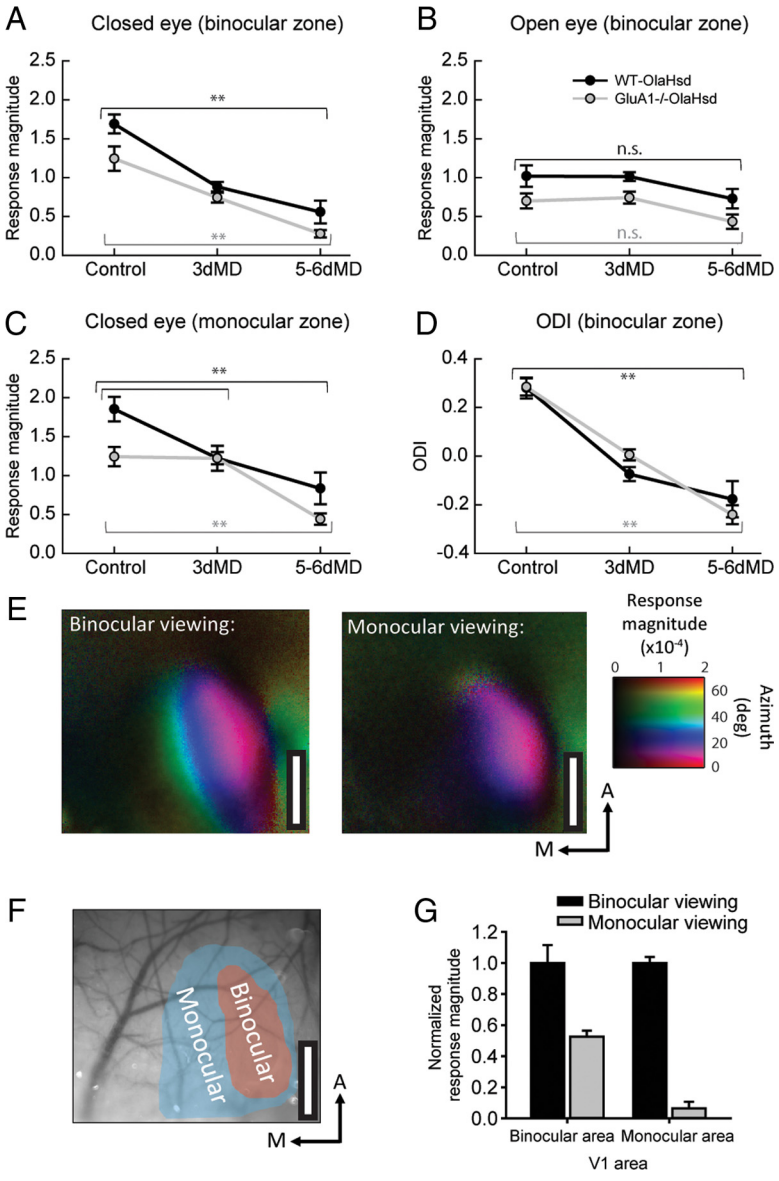

Figure 2. In C57BL/6OlaHsd mice, open eye depression is delayed but not abolished in the monocular zone in the *GluA1*$^{-/-}$ genotype. ISI response magnitudes before and after MD for WT (black line) and *GluA1*$^{-/-}$ (gray line) mice. ***A***, Binocular zone response to contralateral eye stimulation. ***B***, Binocular zone response to ipsilateral eye stimulation. ***C***, Monocular zone response to contralateral eye stimulation. ***D***, Ocular dominance index. Note baseline responses (control, left-most points) are significantly different (***A–C***). Note also that depression is delayed for the MZ but not BZ in *GluA1*$^{-/-}$ mice (**$p < 0.01$; black, WT comparisons; gray, *GluA1*$^{-/-}$ unpaired *t* tests). All absolute response magnitudes are mean $\Delta R/R$ values of the magnitude $\times 10^{-4}$ ± SEM (WT: control, $n = 12$; 3 d MD, $n = 13$; 5–6 d MD, $n = 6$; *GluA1*$^{-/-}$: control, $n = 9$, 3 d MD, $n = 7$; 5–6 d MD, $n = 5$). ***E***, Example response isoazimuth maps to full field stimulation for binocular viewing (left) and monocular viewing (right) through the ipsilateral eye only. Note that response magnitudes are normalized to maximum as measured on the binocular viewing map. (M, medial; A, anterior). ***F***, Green-light image illustrating location of MZ and BZ generated from the thresholded functional maps in ***E*** and ***F***. Scale bars, 1 mm. ***G***, Quantification of visual drive to binocular and monocular areas under binocular (black) and monocular (gray bars) stimulation for 6 WT-OlaHsd mice.

To test for possible differences in visual response in the monocular and binocular zones that might explain the delayed depression in the MZ, we compared visually evoked activity in MZ and BZ of WT-OlaHsd mice, either under normal viewing conditions or with one eyelid occluded acutely to simulate MD conditions (Fig. 2*E*). We found that the response was reduced by 49% in the binocular zone but by 94% in the monocular zone (Fig. 2*G*). The reduction in response for monocular compared with binocular stimulation was significantly greater in the MZ compared with the BZ (paired *t* test, $p < 0.03$, $t = 3.11$), suggesting

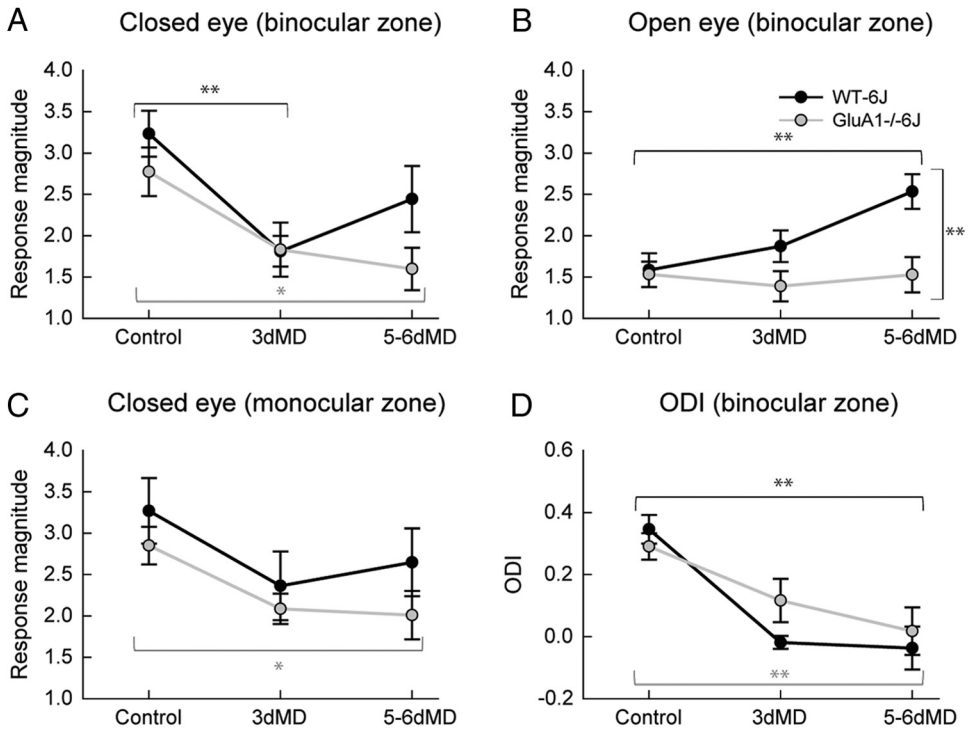

Figure 3. In C57BL/6 mice, open eye potentiation is impaired in *GluA1*$^{-/-}$ genotype. ***A***, Binocular zone response to contralateral eye stimulation. ***B***, Binocular zone response to ipsilateral eye stimulation. ***C***, Monocular zone response to contralateral eye stimulation. ***D***, Ocular dominance index. Response magnitudes before and after MD for WT-6J (black line) and *GluA1*$^{-/-}$*6J* (gray line) mice. Note that depression occurs normally after 3 d MD in the *GluA1*$^{-/-}$*6J* mice but the modest response recovery in WTs at 5–6 d in the closed eye response is clearly absent in *GluA1*$^{-/-}$ mice (***A***) and there is no potentiation of the open eye response (***B***). WT: control, $n = 7$; 3 d MD, $n = 7$; 5–6 d MD, $n = 6$; *GluA1*$^{-/-}$*6J*: control, $n = 7$; 3 d MD, $n = 7$; 5–6 d MD, $n = 7$. Vertical brackets refer to comparisons between genotypes (*t* tests) and horizontal brackets within genotype but between time points. $*p < 0.05$, $**p < 0.01$; black, WT comparisons; gray, *GluA1*$^{-/-}$ (unpaired *t* tests).

that the lower level of activity and lack of competition in the MZ during MD may drive depression at a slower rate in the *GluA1*$^{-/-}$*OlaHsd* mice.

The homeostatic component of OD plasticity is absent in *GluA1*$^{-/-}$*J* mice

A 5–6 d period of MD during the critical period typically results in a significant increase in cortical response to the open eye and moderate recovery of responsiveness to the closed eye (compared with 3 d MD). To test the dependence of this homeostatic process upon GluA1, we generated a line of *GluA1*$^{-/-}$ mice on the C57BL/6J background, which we have previously shown to exhibit robust *in vivo* homeostatic plasticity and synaptic scaling while C57BL/6OlaHsd mice do not (Ranson et al., 2012). We again compared mice lacking GluA1 (*GluA1*$^{-/-}$*6J*) with their WT-6J littermates and found that their baseline responses in the undeprived condition were similar. Unlike responses on the OlaHsd background, *GluA1*$^{-/-}$*6J* showed a smaller average difference in response magnitude compared with WT-6Js (between 5–16% depending upon the stimulus; Fig. 3*A–C*) and again near identical baseline ODI values (Fig. 3*D*; WT-6J: 0.35 ± 0.05; *GluA1*$^{-/-}$*6J*: 0.29 ± 0.04).

The restoration of baseline responses to WT levels in *GluA1*$^{-/-}$*6J* mice is most likely due to breeding out a homeostatic plasticity deficit related to synaptic scaling (Ranson et al., 2012) carried by C57BL/6OlaHsd background mice by crossing with C57BL/6J mice, which have normal synaptic scaling. This interpretation is corroborated by the fact that we see homeostatic plasticity in the WT-6J animals (Fig. 3), as described below.

We examined the effect of MD on ODI in the two genotypes and found that following a 5–6 d period of MD, the ODI shifted in both WT-6J and *GluA1*$^{-/-}$*6J* mice to a similar degree (Fig. 3*D*; WT-6J: −0.04 ± 0.07; *GluA1*$^{-/-}$*6J*: 0.02 ± 0.08). However, the mechanism by which this occurred differed fundamentally between the two genotypes. In WT-6J animals, the ODI shift was primarily due to potentiation of the open eye response, which was highly statistically significant after 5–6 d MD (Fig. 3*B*; WT-6J: shifted from 1.59 ± 0.20 to 2.53 ± 0.21, $p < 0.01$, $t = 3.22$). In contrast, *GluA1*$^{-/-}$ mice on the same background exhibited no open eye potentiation (Fig. 3*B*; open eye potentiation after 5–6 d MD; *GluA1*$^{-/-}$*6J*: from 1.53 ± 0.15 to 1.53 ± 0.21, $p = 0.99$, $t = 0.14$). Consequently, the open eye responses after 5–6 d deprivation differed significantly between WT-6J and *GluA1*$^{-/-}$*6J* ($p < 0.01$, $t = 3.35$). The shift in ODI in the *GluA1*$^{-/-}$*6J* mice was due purely to closed eye depression that was already near-maximal at 3 d MD (Fig. 3*A*). These results strongly support the hypothesis that open eye potentiation during the critical period operates by a GluA1-dependent mechanism.

Normal adult OD plasticity and facilitation of plasticity by prior experience in *GluA1*$^{-/-}$*-OlaHsd* mice

The mouse visual cortex also exhibits a number of forms of OD plasticity in adulthood. First, a 7 d period of altered visual experience causes an OD shift, which is mediated primarily by an increased cortical response to the open eye (Sawtell et al., 2003). Second, if normal visual experience is then resumed, a recovery to a normal OD occurs (Hofer et al., 2006). Finally, if mice are again exposed to monocular visual experience, they will more rapidly undergo an OD shift, requiring only 3 d MD, as opposed to the 7 d MD necessary in naive animals (Hofer et al., 2006). We tested the dependence of these three forms of plasticity on GluA1 in a longitudinal imaging experiment in which animals were imaged

after the first MD (7 d), following recovery from MD and after a second shorter MD (3 d). We found that adult WT-OlaHsd and adult *GluA1*$^{-/-}$*-OlaHsd* mice exhibited remarkably similar plasticity profiles during the three OD shifts with no statistically significant differences observed between *GluA1*$^{-/-}$*-OlaHsd* and WT-OlaHsd littermates at any time-point (Fig. 4). These data suggest that the importance of GluA1 in visual cortex plasticity is limited to the postnatal critical period.

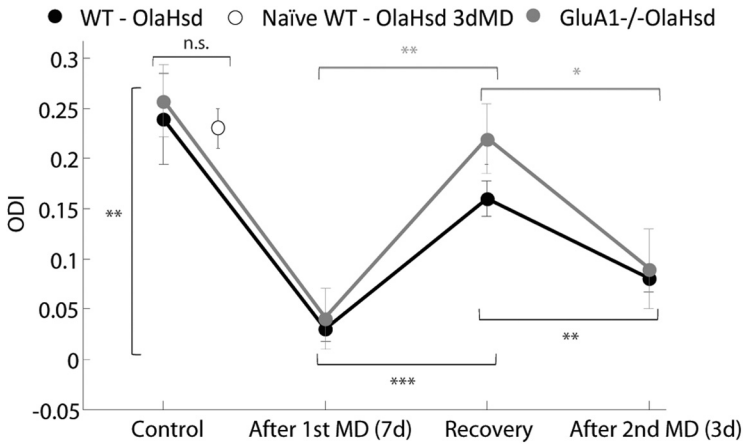

Figure 4. Studies of adult plasticity in WT (black) and *GluA1*$^{-/-}$ (gray) mice after a conditioning monocular deprivation during the critical period (OlaHsd background). In all cases, we found a large effect of opening or closing the ipsilateral eye, but no difference between genotypes. The control and first MD time points show the effect of a conditioning 7 d MD period in adulthood (ANOVA: effect of deprivation, $t = 6.68$, $p < 0.0001$; no effect of genotype, $t = 0.43$, $p = 0.68$, unpaired comparison, WT: control, $n = 12$; 3 d MD, $n = 13$; *GluA1*$^{-/-}$: control, $n = 9$; 3 d MD, $n = 7$). The second, third, and fourth time points show the effect of 4 weeks recovery followed by a second 3 d MD period. Once again, we found no differences between genotypes (ANOVA: no effect of genotype, $t = 1.58$, $p = 0.22$; effect of monocular/binocular vision, $t = 20.08$, $p < 0.0001$). Comparison of the second and third time point (same animals) show the recovery produced by restoring binocular vision (WT: $t = 8.39$, $p < 0.0004$; *GluA1*$^{-/-}$: $t = 5.5$, $p < 0.01$, paired *t* tests). Comparison of the third and final time point (same animals) show the effect of 3 d MD, which normally has no effect in a naive adult animal (open circle data point near control data at the left), but does cause a shift in ODI following a conditioning MD during the critical period (WT: $t = 2.37$, $p < 0.05$; *GluA1*$^{-/-}$: $t = 4.41$, $p < 0.001$, paired *t* tests). Note that for adult experiments, WT control $n = 5$, while six animals were imaged repeatedly for the remainder of the time points; *GluA1*$^{-/-}$*OlaHsd* control $n = 4$, while five animals were imaged repeated for the remainder of the time points. ***$p < 0.001$, **$p < 0.01$; *$p < 0.05$.

Discussion

Homeostatic potentiation mechanisms

The main finding of this study is that GluA1 is necessary for potentiation of open eye responses during the critical period for OD plasticity, but not later in adulthood. The requirement for GluA1 therefore parallels the requirement for TNFα at the two ages, as the potentiation component of plasticity has also been shown to depend on TNFα during the critical period (Kaneko et al., 2008), but not in adulthood (Ranson et al., 2012). Cell surface expression of GluA1 is increased by TNFα and decreased by "decoy" soluble TNF receptors (Stellwagen et al., 2005), which suggests that GluA1 is the effector molecule used by a homeostatic plasticity process mediated by TNFα. This idea is consistent with the finding that GluA1 is required for homeostatic synaptic scaling in the visual cortex (Goel et al., 2011).

We also found that in a background strain lacking synaptic scaling (C57BL/6OlaHsd), normal V1 responses were lower in the cortex in undeprived *GluA1*$^{-/-}$ mice than in their wild-type litter-mates. This effect could not be attributed to lower responses in the retina or reduced thalamic input to cortical layer 4, suggesting that GluA1 contributes either to direct thalamic input to layer 2/3 or to excitatory intracortical transmission. However, on breeding the *GluA1 knock-out* mouse into a background strain that does show synaptic scaling (C57BL/6J), response levels were restored to wild-type levels in the *GluA1*$^{-/-}$ mice. This implies that a second GluA1 independent homeostatic mechanism must also operate in the cortex but that it is not engaged in the homeostatic responses to monocular deprivation.

A feasible candidate for a second homeostatic mechanism is one that operates via GluA2 rather than GluA1 (Gainey et al., 2009; Altimimi and Stellwagen, 2013; Lambo and Turrigiano, 2013). The main evidence comes from experiments in which TTX is applied to cultured cortical neurons leading to up-scaling of mEPSPs. If shRNA for GluA2 is applied to the cell cultures, it blocks the TTX-driven up-scaling, as does a peptide designed to interfere with the C-terminal tail of GluA2 (Gainey et al., 2009). In contrast, a peptide designed to interfere with GluA1 does not affect TTX-induced scaling (Gainey et al., 2009). This suggests that the GluA2-dependent scaling mechanism could be the second homeostatic mechanism responsible for the difference in response levels in the cortex of *GluA1*$^{-/-}$*6J* versus *GluA1*$^{-/-}$*OlaHsd* mice.

LTP-like potentiation mechanisms

GluA1 is involved in a postsynaptic component of LTP in the barrel cortex (Hardingham and Fox, 2006; Hardingham et al., 2008), where it appears to be related to experience-dependent potentiation (Dachtler et al., 2011). GluA1 has also been shown to contribute a component of LTP in the hippocampus (Hoffman et al., 2002; Phillips et al., 2008), though a recent study has highlighted differences in the role of GluA1 in hippocampus and visual cortex (He et al., 2011). The mechanism we describe here for GluA1-dependent potentiation in the visual cortex during the critical period may not be related to LTP however, because LTP is present in animals that completely lack open-eye potentiation; for example, TNFα knock-out mice exhibit LTP in the visual cortex (Kaneko et al., 2008) and *GluA1*$^{-/-}$ mice exhibit LTP in the hippocampus (Phillips et al., 2008) and barrel cortex (Hardingham and Fox, 2006; Hardingham et al., 2008), albeit an attenuated form.

We have previously argued that adult plasticity in the visual cortex is likely to act via a mechanism more akin to LTP, based on the fact that it is not dependent on TNFα but is dependent on CaMKII autophosphorylation (Ranson et al., 2012). It may seem curious, therefore, that the adult plasticity mechanism we describe here does not require GluA1. The canonical explanation for LTP is that GluA1 homomeric AMPA receptors are inserted into the postsynaptic site dependent on multiple phosphorylation of elements on its C-terminal domain. However, recent studies show that the GluA1 C-terminal domain is not absolutely necessary for LTP (Granger et al., 2013) and could point to other GluA1-independent forms of LTP.

Binocular zone depression mechanisms

We found a lack of effect of GluA1 on depression in the binocular zone of the visual cortex. This is consistent with previous reports

showing that depression of responses to deprived eye stimulation is mediated via a cannabinoid receptor system (Liu et al., 2008). Interestingly, only layer 2/3 depression is cannabinoid dependent, while layer 4 depression occurs normally in the presence of cannabinoid antagonists (Liu et al., 2008). The layer 4 depression mechanism appears to be GluA2-dependent (Yoon et al., 2009). Because our measurements using ISI directly measure responses mainly in layer 2/3 and only indirectly those in layer 4 (on which L2/3 responses depend to some extent), our results suggest that GluA1 knock-out does not interfere with these depression processes in binocular visual cortex.

Monocular zone depression mechanisms

In the monocular zone, depression in *GluA1 knock-out* mice on the OlaHsd background was delayed. A plausible explanation for this finding is that in mice lacking GluA1, depression of the closed eye is already partially occluded in the undeprived condition but that some further depression can occur by GluA1 independent (cannabinoid-dependent) mechanisms. In contrast, in mice possessing GluA1, depression may be able to occur by both a GluA1-dependent and GluA1-independent mechanism. The difference in the rate of plasticity between binocular and monocular areas appears to be due to the significant differences in visual drive and thus spiking activity during MD of binocular versus monocular cortex (Fig. 2*E–G*).

In conclusion, while some details of the mechanisms of closed eye depression remain to be elucidated in the visual cortex, the mechanism by which open eye potentiation occurs is becoming clearer. The present results provide evidence that GluA1 is required for open eye potentiation and is most likely inserted in the postsynaptic membrane of neurons in response to TNFα released from glial cells (Stellwagen and Malenka, 2006), which is in turn due to a reduction in activity owing to the closed contralateral eye.

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