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ORIGINAL ARTICLE

Social hierarchy regulates ocular dominance plasticity in adult male mice

Jenny Balog[1] · Franziska Hintz[2] · Marcel Isstas[1] · Manuel Teichert[1] · Christine Winter[2] · Konrad Lehmann[1,3]

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Abstract

We here show that social rank, as assessed by competition for a running wheel, influences ocular dominance plasticity in adult male mice. Dominant animals showed a clear ocular dominance shift after 4 days of MD, whereas their submissive cagemates did not. NMDA receptor activation, reduced GABA inhibition, and serotonin transmission were necessary for this plasticity, but not sufficient to explain the difference between dominant and submissive animals. In contrast, prefrontal dopamine concentration was higher in dominant than submissive mice, and systemic manipulation of dopamine transmission bidirectionally changed ocular dominance plasticity. Thus, we could show that a social hierarchical relationship influences ocular dominance plasticity in the visual cortex via higher-order cortices, most likely the medial prefrontal cortex. Further studies will be needed to elucidate the precise mechanisms by which this regulation takes place.

Keywords Social dominance status · Ocular dominance plasticity · Primary visual cortex · Medial prefrontal cortex · Optical imaging · Serotonin · GABA · NMDAR · Dopamine

Introduction

Dominance and submissiveness occur in all areas of life, not only among people in school, work and other social situations, but in all group living animals (Stears et al. 2014). The physiological background of this social condition is being studied in many vertebrate (Morgan et al. 2002; Desjardins and Fernald 2008; Kar et al. 2017; Jetz and Rubenstein 2011), and invertebrate species (Sbragaglia et al. 2017). A social hierarchy entails a dominant–submissive relationship between all individual pairs of animals within the group. As a result, most animals will experience defeat and subordination frequently. In rodents, this experience has been shown to induce stress (Blanchard et al. 1995), compromise mental health (Prabhu et al. 2018), and impair learning (Goeckner et al. 1973; Spritzer et al. 2004). More recent studies in pairs of mice have confirmed that, indeed, learning ability deteriorates in submissive animals, which is not, however, directly due to stress (Fitchett et al. 2005; Colas-Zelin et al. 2012; Matzel et al. 2017).

Though an impact of social dominance or submissiveness on behavioural learning has thus been well established, an effect on more basal cortical plasticity has not yet been investigated. We have recently shown that paired, in contrast to individual, housing of adult mice reinstated ocular dominance plasticity (ODP, Balog et al. 2014), i.e., the propensity of the primary visual cortex (V1) to shift its responsiveness towards the open eye when one eye is experimentally closed. While in female mice, which are not aggressive and do not establish a clear hierarchy, this effect was seen irrespective of the available space, it was only present in both male mice of a pair if they disposed of a large arena. In a standard cage, only one of the two would show plasticity.

The assumption was obvious that the difference in plasticity was due to social dominance, the cramped space forcing the males to arrange their relationship differently than in the large arena. In this study, we tested this hypothesis and went on to elucidate the mechanisms by which social status regulates ODP in male mice. In addition to biochemical factors acting within the visual cortex, we found dopamine, acting

✉ Konrad Lehmann
Konrad.Lehmann@uni-jena.de

[1] Institut für Allgemeine Zoologie and Tierphysiologie, Friedrich Schiller-Universität Jena, Erbertstr. 1, 07743 Jena, Germany

[2] Department of Psychiatry and Psychotherapy, Charité University Medicine Berlin, Berlin, Germany

[3] GSI Helmholtzzentrum für Schwerionenforschung GmbH, Abteilung Biophysik, Darmstadt, Germany

most probably in the prefrontal cortex, to play a decisive role.

Materials and methods

Animals and housing conditions

Fully adult (> postnatal day 133) male C57BL/6J mice were housed in groups of 2–3 in transparent standard Makrolon cages (16.5 × 22.5 cm^2, minimally enriched with cotton rolls and nest material) on a 12 h light/dark cycle, with food and water available ad libitum. The selected mice were on average 364 days old, with an average age difference of 12 days (median: 11 days) within pairs. The experiment started with joining two animals out of different groups into one standard cage. Beginning immediately, the animals got access to a running wheel for 1.5 h per day during 3 days before and after MD, to assess dominance behaviour (see below). In the arena condition, two mice together were kept 6 h per day in a square, featureless arena with a side length of 72 cm, and were then put back into their single cages.

All groups, including the control group animals, were treated identically as described above. In our institution, animal housing is constantly supervised by veterinaries from the state of Thuringia, Germany. All experimental procedures have been performed according to the German Law on the Protection of Animals and the corresponding European Communities Council Directive of 2010 (2010/63/EU), and were approved by the Thüringer Landesamt für Lebensmittelsicherheit und Verbraucherschutz (Thuringia State Office for Food Safety and Consumer Protection) under the registration number 02-036/15.

Behavioural analysis

Male mice are territorial and will form a dominance hierarchy when forced to live together (Kappel et al. 2017). For obvious animal welfare reasons, we could not maintain pairings in which escalating fighting was observed. In peaceful mice, however, dominance hierarchy is hard to determine after its initial agonistic establishment. We therefore developed several behavioural criteria for the reliable determination of social dominance.

First, whenever possible, we arranged pairings in which one of the mice lacked the vibrissae, since they were likely the victims of so-called "barbering" by dominant mice in their group of origin (Sarna et al. 2000), and therefore possibly predisposed for becoming submissive again.

Second, we routinely assessed competition for a limited resource in all pairings. For mice, use of a running wheel is so desirable that they will even access it in the wild (Meijer and Robbers 2014). Indeed, when the pairing cage was furnished with just one running wheel, it became quickly apparent which mouse asserted privileged access to it. Although it has been claimed that running wheel use during MD can by itself elicit ODP (Kalogeraki et al. 2014), we have previously conclusively shown that locomotion or running wheel use has no such effect during short-term MD of single or paired housed mice (Balog et al. 2014). Potential reasons for the discrepancy will be dealt with in the discussion.

Thus, we provided a running wheel to both animals together for 3 days before and after monocular deprivation for 1 h per day. Turns run by each mouse were counted automatically, converted into m/h and averaged across days. To ensure that differential use of the running wheel was not due to differing interest, each mouse was subsequently put alone for 1/2 h into a running wheel cage, and turns were counted. Running wheel use alone and in pairs could then be quantitatively compared.

Third, to corroborate that running wheel use is a reliable measure of social dominance, we also performed a behavioural analysis by counting behaviours defined in an ethogram based on a published template (Olsson and Sherwin 2006). The following behaviours were counted while the mice were together in the running wheel cage:

Attack—jumping at or chasing the other mouse, biting, kicking, wrestling.
Flight—avoidance of contact, direct withdrawal from the other mouse.
Head sniff—sniffing directed to the head (mostly nose) of the other mouse.
Anal sniff—sniffing directed to the anus of the other mouse.
Social grooming—licking and nibbling the other mouse at different areas of the body.
Allogrooming—more intense grooming: vigorous licking with a higher incidence of teeth or hair pulling. The other mouse is usually motionless, otherwise it comes to a fight.

Monocular deprivation

Monocular deprivation was always performed after the first imaging session according to published protocols (Gordon and Stryker 1996; Lehmann et al. 2012). Briefly, mice were anaesthetized by 2% isoflurane in a mixture of 1:1 N_2O and O_2. Before the imaging session, animals received one injection of carprofen (4 mg/kg, s.c.) as an analgesic and anti-inflammatory agent. Lid margins of the right eye were trimmed and an antibiotic ointment was applied before the eye was sutured shut. All animals were checked daily to ensure that the sutured eye remained closed during the 4 days of MD. Over the following days, animals received a daily administration of carprofen (0.12 mg/mouse, s.c.).

Drug administration

WAY-100635

To investigate if serotonin plays a role for the restored ODP, we administrated 1 mg/kg i.p. of the 5-HT_{1A}-receptor antagonist WAY-100635, diluted in saline (Fletcher et al. 1996; Forster et al. 1995).

Diazepam

To test if changes in the activity of GABA are necessary to trigger adult ODP, we treated the animals with a daily i.p. injection of 1 mg/kg diazepam (Stodieck et al. 2014).

CPP

To find out the role of the *N*-methyl-D-aspartate (NMDA)-receptor on ODP, we administrated the NMDA receptor antagonist (R,S)-3-(2-carbooxypiperazin-4-yl)propyl-1-phosphonic (CPP) at a daily dose of 12–15 mg/kg i.p. in saline (Sato and Stryker 2008; Villarreal et al. 2002).

Zuclopenthixol

To investigate a possible role of cortical dopamine transmission in ODP, we treated the animals with the dopamine receptor (D1 and D2) antagonist zuclopenthixol at a low dose that reduces aggression without motor effects (Manzaneque and Navarro 1999). It was diluted in methylcellulose (15% in aqua bidest) and 15% ethanol and injected i.p. every 24 h at a dose of 0.2 mg/kg.

Methylphenidate

To enhance cortical dopamine transmission, we administrated the dopamine reuptake inhibitor methylphenidate hydrochloride at a low dose that increases dopamine transmission only in the mPFC but not the striatum (Koda et al. 2010). It was diluted in 0.9% NaCl and injected four times a day at a dose of 3 mg/kg.

Optical imaging of intrinsic signals

Mouse preparation for optical imaging

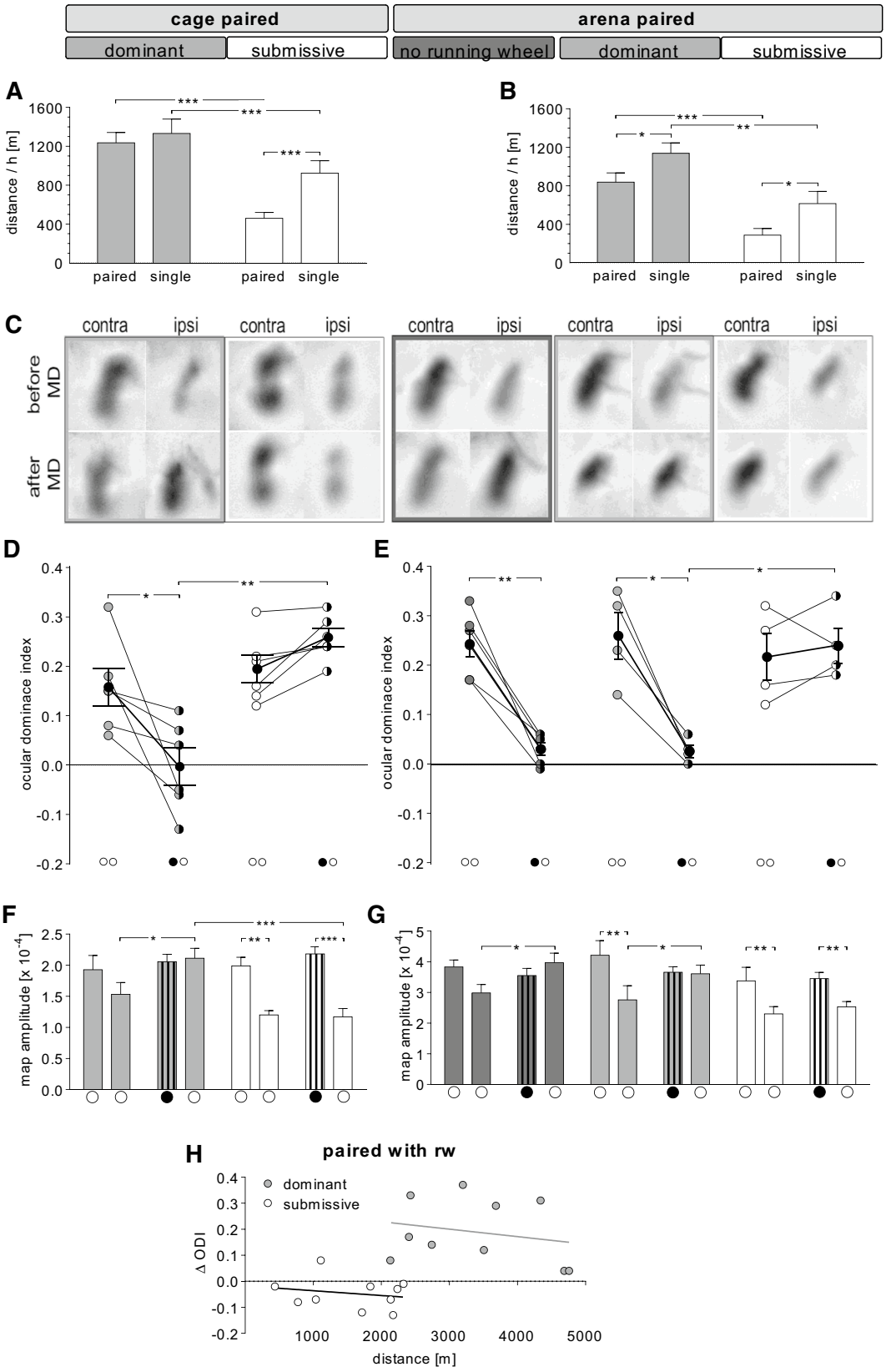
Animals were initially anaesthetized with 4% isoflurane in a mixture of 1:1 O_2/N_2O and placed on a heating blanket (37.5 °C) for maintaining body temperature. They then received injections of chlorprothixene (0.2 mg/mouse, i.m.), atropine (0.3 mg/mouse, s.c.), dexamethasone (0.2 mg/mouse, s.c.) and carprofen (0.12 mg/mouse, s.c.). Inhalation anaesthesia was applied through a plastic mask and maintained at 1.5% during the surgical intervention and 0.5% during data recording. The animal was fixed in a stereotaxic frame using non-crush ear bars. The skin above the left hemisphere was removed to expose the visual cortex. This exposed area was covered with 2.5% agarose in saline and sealed with a glass coverslip. Cortical responses were always recorded through the intact skull. Immediately after the first imaging session the skin was resutured and MD was performed. After that, the animals were returned to their standard cage which was placed on a heating plate overnight. Mice were checked every 15 min until the righting reflex was positive. Before the next imaging session, the skin and the eye were reopened and imaging was performed as described above.

Imaging of visual cortex

The imaging method of temporally encoded maps was originally described by Kalatsky and Stryker (2003). Using a Dalsa 1M30 CCD camera (Dalsa, Waterloo, Canada) with a 135 mm × 50 mm tandem lens configuration (Nikon, Inc. Melville, NY, USA), we imaged an area of 4.6 × 4.6 mm^2. The surface vascular pattern was visualized by green illumination (550 ± 2 nm). Thereafter, focusing 600 µm below the pial surface, intrinsic signals were obtained via illumination with red light (610 ± 2 nm). Frames were acquired at a rate of 30 Hz and temporally averaged to 7.5 Hz. The 1024 × 1024 pixel images were spatially binned to a 512 × 512 resolution. Horizontal drifting bars (2° wide) were presented at a temporal frequency of 0.125 Hz and were adjusted so that they only appeared in the binocular visual field of the recorded left hemisphere (− 5° to + 15° azimuth). Thus, the stimulus was repeated for about 35 times during one presentation. Cortical responses were extracted by Fourier analysis at the stimulation frequency and converted into amplitude and phase maps using custom software (Kalatsky and Stryker 2003). Ocular dominance indices (ODIs) were calculated from activity maps as described previously (Cang et al. 2005; Lehmann and Löwel 2008). Briefly, within a region of interest, all pixels above a threshold at 30% of peak amplitude were used, and OD was calculated for each pixel as (contra − ipsi)/(contra + ipsi), and averaged across all selected pixels.

Post-mortem HPLC

After the second session of optical imaging, the scalp was sutured and the animals were allowed to re-awake. The following day, they were again transferred to their respective condition for another 3 days. After that, the animals were killed by cervical dislocation, the brains were quickly dissected and frozen immediately at − 40 °C. Neurotransmitter contents were measured using high-performance liquid


cage paired
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◂**Fig. 1** Social dominance determines ODP. Both in a cage (**a**, $p \leq 0.001$, $n = 6$) and in an arena (**b**, $p \leq 0.001$, $n = 3$), a running wheel is predominantly used by only one of two male animals. When alone, the less active animals significantly increase running (cage: $p \leq 0.001$; arena: $p \leq 0.05$). **c** Amplitude maps obtained by optical imaging of intrinsic signals are shown. While stronger activities are always elicited by stimulation of the contralateral than the ipsilateral eye before MD, this difference is lost or even reversed in dominant cage paired ($n = 6$) and arena paired mice ($n = 3$) or arena mice without a running wheel ($n = 6$). **d** In a cage, dominant mice showed ODP after 4 days of MD ($p \leq 0.05$, $n = 6$), whereas submissive mice did not ($p = 0.7$, $n = 6$). **e** When housed in the arena, all mice (w/o rw: $p \leq 0.01$, $n = 6$ and rw: $p \leq 0.05$, $n = 4$) showed full plasticity, but once social hierarchy was induced by the presence of a running wheel, ODP disappeared in submissive animals ($p = 1$, $n = 4$). Each symbol represents the ODI of an individual animal, horizontal lines show the group mean. Full symbols represent control measurements, half symbols measurement after MD. White circles show open eyes, black circles closed contralateral eyes. Dominant animals are shown as grey, submissive animals as white symbols. **f**, **g** V1 activity elicited by contra- (left-hand bars) or ipsilateral (right-hand bars) eye stimulation (shadings as in **d** and **e**, hatching indicates deprived eyes) shows that ODP was achieved by open-eye potentiation in dominant cage mice ($p \leq 0.05$, $n = 6$), in arena mice without running wheel ($p \leq 0.05$, $n = 6$), and in dominant arena mice with running wheel ($p \leq 0.05$, $n = 4$, all comparisons by Tukey test). **h** Running activity had no influence on ODP (ODI before MD–ODI after MD) neither in submissive ($p = 0.57$, $n = 10$) nor in dominant mice ($p = 0.54$, $n = 10$)

chromatography (HPLC). Micropunches were taken from 1 mm mPFC slices at 2.34 from Bregma and 1 mm V1 slices at − 3.28 from Bregma (Paxinos and Franklin 2012). These brain samples were homogenized by ultrasonication in 20 vol of 0.1 N perchloric acid at 4 °C immediately after collection. A total of 100 µl of the homogenate was added to equal volumes of 1 N sodium hydroxide for measurement of protein content. The remaining homogenate was centrifuged at 17,000*g* and 4 °C for 10 min. Supernatants were used for immediate measurement. The levels of monoamines (DA and 5-HT) and their metabolites (DOPAC, and 5-HIAA) were measured by HPLC with electrochemical detection as previously described (Felice et al. 1978; Sperk et al. 1981; Sperk 1982; Enard et al. 2009; Winter et al. 2009; Giovanoli et al. 2013). Briefly, the perchloric acid extracts were separated on a column (Prontosil 120-3-C18-SH; length 150 mm, inner diameter 3 mm; Bischoff Analysentechnik und -geräte GmbH, Leonberg, Germany) at a flow rate of 0.55 ml/min. The mobile phase consisted of 80 mM sodium dihydrogen phosphate, 0.85 mM octane-1-sulfonic acid sodium salt, 0.5 mM ethylenediaminetetraacetic acid disodium salt, 0.92 mM phosphoric acid and 4% 2-propanol (all chemicals Merck KGaA, Darmstadt, Germany). Monoamines were detected using an electrochemical detector (41,000, Chromsystems Instruments and Chemicals GmbH, Munich, Germany) at an electrode potential of 0.8 V. For calibration, 0.1 M perchloric acid containing 0.1 mM DOPAC, 5-HIAA and 5-HT and 1 mM DA was injected into the HPLC system before and after sample analysis. Sample analysis was performed based on peak areas using a computer-based chromatography data system (CSW 1.7, DataApex Ltd, Prague, Czech Republic) in relation to the mean of the applied calibration solutions.

Retrograde fluorescent tracing

Mice were prepared for optical imaging (see above), and one map of absolute retinotopy was acquired in the left hemisphere. The map was overlaid over an image of the blood vessel pattern. Trepanations were performed over the parts of the visual cortex that represented the upper and the lower visual field. A green retrograde tracer (CTb-488) was injected into the rostral, a red tracer (Ctb-594) into the caudal visual cortex. Then, the scalp was sutured, and the animal was allowed to wake up.

1 week later, the animal was perfused with 0.1 M PBS, followed by 4% PFA in PBS. The brain was dissected and frozen after cryoprotection. 50 µm slices were taken on a vibratome, counterstained with DAPI and coverslipped with Mowiol.

Statistical analysis

All group comparisons were initially subjected to one- or two-way ANOVA, with repeated measures where appropriate, to check for main effects. Post hoc analysis was done by Tukey tests, which are insensitive to deviations from normal distribution. Paired comparisons were performed by Wilcoxon signed-rank test. The levels of significance were set as $*p \leq 0.05$; $**p \leq 0.01$; $***p \leq 0.001$. Data are presented as means and standard error of the mean (s.e.m.).

Results

Running wheel use reflects and induces the expression of social hierarchy in mice

Having previously shown that of a pair of male mice housed in a standard cage, only one will show ocular dominance (OD) plasticity after 4 days of MD (Balog et al. 2014), we here wished to test our hypothesis that this difference is due to a social hierarchy. To this end, we established a novel dominance test: the mice got access to a running wheel, both together (1 h/day) and alone (1/2 h/day), 3 days before and 3 days during MD. Figure 1a shows running wheel use of mice classified as "dominant" (grey columns) or "submissive" (white columns) both while together and while alone. In each pair, one mouse each was assigned to either group based on these measures. While being together in the running wheel cage, dominant mice accessed the running wheel significantly more (1235.83 ± 106.63 m/h) than

their submissive cagemates (458.78 ± 63.94 m/h, $p \leq 0.001$, $n = 12$). When the animals were alone, this difference between dominant and submissive animals did not disappear ($p \leq 0.001$), but submissive mice drastically increased their use of the wheel (923.36 ± 132.69 m/h, $p \leq 0.001$, compared to paired), whereas dominant mice did not (1331.96 ± 148.20 m/h, $p = 0.5$, compared to paired). This shows that mice classified as submissive did not lack interest in the wheel, but refrained from its use because the dominant mouse was present.

Ethological data corroborated this interpretation. In all cases, mice classified as dominant because of the running wheel data performed attacks at a much higher rate—usually exclusively—than the submissive mice, which correspondingly showed flight behaviour. Frequently, submissive mice were chased from the wheel by their dominant cagemates. In all cases, these observations confirmed the ranking derived from wheel use.

We have previously shown that paired male mice in a featureless arena differ significantly in their behaviour from pairs in a cage, and both show ODP at an indistinguishable level (Balog et al. 2014). This indicates that social hierarchy is not established in the absence of a limited resource. To test this assumption, we introduced a running wheel into an otherwise bare arena. Indeed, its use by the two mice was disbalanced, with one animal occupying it most of the time and defending the access violently, yielding very similar results to the cage condition (dominant paired 838.32 ± 96.27 m/h vs. submissive paired 288.01 ± 68.58 m/h, $p \leq 0.001$; dominant single 1137.93 ± 108.55 m/h vs. submissive single 614.87 ± 126.99 m/h, $p \leq 0.01$, $n = 8$). The mice were accordingly classified as "dominant" and "submissive" (Fig. 1b). This classification was not influenced by age ($p = 0.54$) nor body weight ($p = 0.97$, Wilcoxon paired signed-rank test, $n = 39$ pairs). We proceeded to test whether the behavioural differences would result in different brain plasticity.

The dominance status of adult male mice regulates ODP

Ocular dominance was measured in the same cage mice before and after 4 days MD via optical imaging (Fig. 1c, d). At control imaging, darker activity spots were always obtained by stimulation of the contralateral than ipsilateral eye (Fig. 1c), and dominant (0.16 ± 0.04) and submissive (0.19 ± 0.03) mice had on average similar OD values ($p = 0.9$, $n = 12$). After 4 days of MD, however, there was a significant OD shift towards the open ipsilateral eye in dominant mice (0.16 ± 0.04 to − 0.003 ± 0.04, $p \leq 0.05$, $n = 6$), whereas the ODI even increased in submissive animals, but not significantly (0.19 ± 0.03–0.26 ± 0.02, $p = 0.6$, $n = 6$, Fig. 1d). ANOVA with repeated measures revealed significant influences of social dominance ($F_{1.10} = 22.542$, $p \leq 0.001$) and its interaction with MD ($F_{1.10} = 12.483$, $p \leq 0.01$). Post hoc Tukey tests confirmed significant differences between dominant and submissive cage mice after MD ($p \leq 0.01$, $n = 12$).

To our surprise, the same difference in plasticity was seen in arena mice after the introduction of a running wheel (Fig. 1c, e). First, we confirmed our previous finding that in a bare arena, both male animals show full ODP. Indeed, the ODI shifted towards lower values in all animals, on average from 0.24 ± 0.03 to 0.03 ± 0.01 after MD ($p \leq 0.01$, $n = 6$). If in the same situation a running wheel was present, leading to the behavioural expression of a social hierarchy (see above), ODP likewise differed between the two animals of a pair, indicated by significant effects of MD (ANOVA, $F_{1.6} = 12.798$, $p \leq 0.05$) and its interaction with social dominance ($F_{1.6} = 18.871$, $p \leq 0.01$). Post hoc Tukey tests showed that in dominant arena mice, there was a significant OD shift (0.26 ± 0.05–0.03 ± 0.01, $p \leq 0.05$, $n = 4$), which was absent in submissive mice (0.22 ± 0.05–0.24 ± 0.04, $p = 0.9$, $n = 4$). Accordingly, the submissive animals had significantly higher OD values after MD than dominant animals ($p \leq 0.05$). Thus, the introduction of a running wheel for only 1 week altogether made visible a social hierarchy that resulted in differential ocular dominance in male mice. Since behavioural and physiological data were similar in cage and arena mice with a running wheel, the respective dominant and submissive groups were pooled for the later biochemical investigations.

Running by itself has been indicated to induce ODP in some studies (Kalogeraki et al. 2014, 2016, 2017). As we have employed running wheel use—albeit only for a short time per day—to assess social dominance, one might argue that the difference in ODP between dominant and submissive mice could trivially be explained by their different amounts of running. Although we have already refuted this assumption in our previous study (Balog et al. 2014), we wished to further check this possibility by correlating the total running distance of each animal with its plasticity, i.e., the difference between ODIs before and after MD (Fig. 1h). Cage and open-field mice were pooled. Although, as expected, all submissive mice are in the lower left quadrant, and all dominant ones in the upper right, which would obviously result in a positive and significant correlation, no such correlation is observed within each group (dominant: $r = -0.22$, $p = 0.54$; submissive: $r = -0.21$, $p = 0.57$, regression analysis). Note, too, the overlap at approx. 2200 m running distance, which does not entail an overlap in plasticity. Thus, brief running for 1.5 h per day during 4 days of MD does not induce ODP in adult male mice.

We wondered whether the observed OD shifts in dominant animals were due to an increase in open-eye activity (so-called adult plasticity) or a decrease in closed-eye activity (juvenile plasticity). In caged pairs, the OD shift of the dominant animal was achieved by strengthening of the

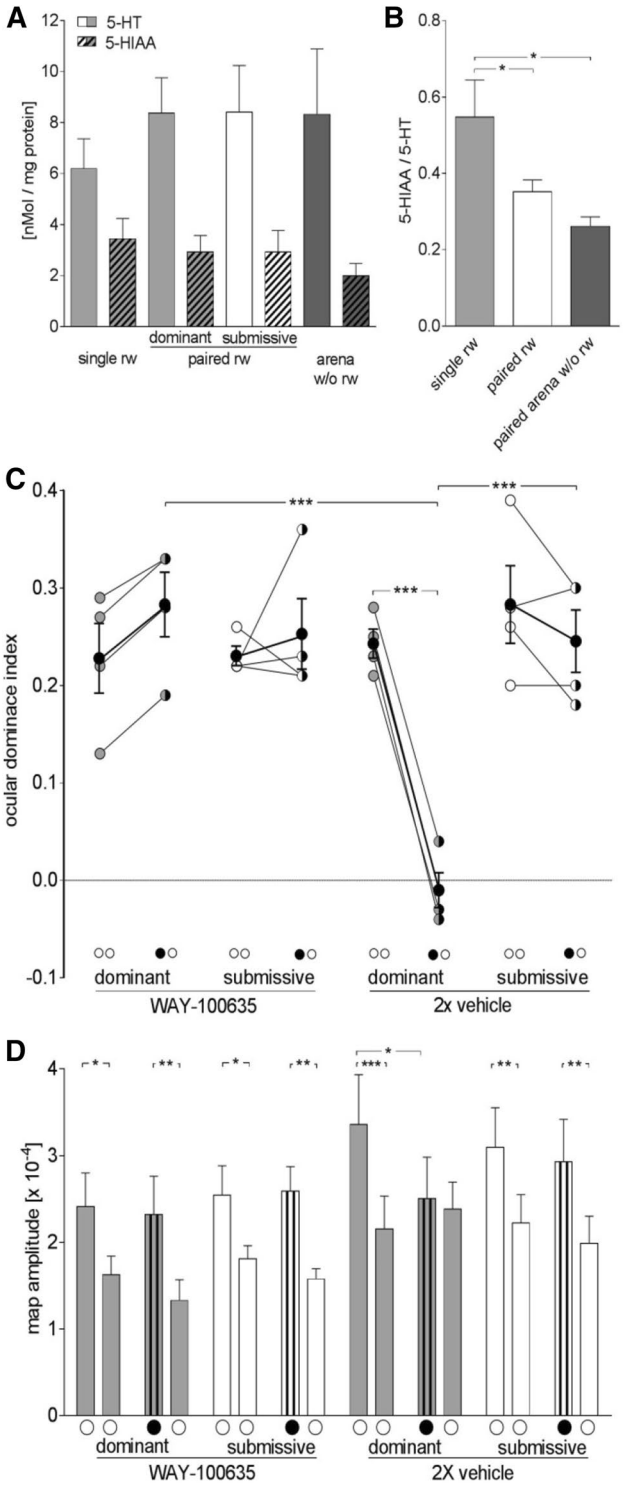

Fig. 2 Adult ocular dominance plasticity induced by social experience requires 5-HT_{1A} receptor activation. **a** The contents of serotonin (5-HT) and its metabolite 5-HIAA were determined by HPLC in the visual cortices. There was no difference in 5-HT or 5-HIAA content between paired dominant and submissive cage mice ($p=1$, $n=18$). **b** 5-HT turnover (5HIAA/5-HT ratio) was significantly higher in single cage mice ($p\leq0.05$, $n=5$) than in paired mice groups with rw ($n=18$) or paired mice without rw (n=4). **c** Ocular dominance indices show that there is no ocular dominance plasticity in dominant paired cage mice treated with the 5-HT_{1A} receptor antagonist WAY-100635 ($p=0.3$, $n=4$), whereas full plasticity was observed in dominant vehicle-injected animals ($p\leq0.001$, $n=4$). **d** Vehicle-treated dominant animals show significant attenuation of the closed contralateral eye response ($p\leq0.05$, $n=4$), while submissive vehicle animals showed no difference of ipsilateral ($p=1$, $n=4$) or contralateral ($p=1$, $n=4$) response before and after 4 days MD. All conventions are as in Fig. 1

ipsilateral (open)-eye input (Fig. 1f, ipsi: $[1.53\pm0.19]\times10^{-4}$ to $[2.11\pm0.16]\times10^{-4}$; $p\leq0.05$, contra: $[1.93\pm0.23]\times10^{-4}$ to $[2.06\pm0.12]\times10^{-4}$; $p=1$, $n=6$). The response amplitudes of contralateral (closed) and ipsilateral (open) eyes of the submissive mice did not change after 4 days MD (ipsi: $[1.2\pm0.07]\times10^{-4}$ to $[1.17\pm0.13]\times10^{-4}$; $p=1$; contra: $[1.99\pm0.14]\times10^{-4}$ to $[2.18\pm0.11]\times10^{-4}$; $p=0.9$, $n=6$).

In the arena (Fig. 1g), ODP was also of the adult type in the control condition, with a significant increase in the open ipsilateral eye response after 4 days of MD ($[2.98\pm0.72]\times10^{-4}$ to $[3.97\pm0.94]\times10^{-4}$, $p\leq0.05$, $n=6$) and no change in the contralateral eye response ($[3.83\pm0.26]\times10^{-4}$ to $[3.55\pm0.29]\times10^{-4}$, $p=0.8$). In the presence of a running wheel, only changes in open (ipsi) eye amplitudes were observed in dominant animals (ipsi: $[2.76\pm0.46]\times10^{-4}$ to $[3.61\pm0.28]\times10^{-4}$, $p\leq0.05$; contra $[4.18\pm0.49]\times10^{-4}$ to $[3.66\pm0.18]\times10^{-4}$, $p=0.3$, $n=4$). The response amplitudes of contralateral and ipsilateral eyes of the submissive mice did not differ after 4 days MD (ipsi: $[2.30\pm0.24]\times10^{-4}$ to $[2.53\pm0.17]\times10^{-4}$, $p=1$; contra $[3.38\pm0.44]\times10^{-4}$ to $[3.45\pm0.2]\times10^{-4}$, $p=1$, $n=4$). Note that ongoing experimental improvement reduced the variance and increased the amplitudes from cage to arena groups.

Thus, presentation of a running wheel induces dominant and submissive behaviour in pairs of male mice, which leads to suppressed ODP in the submissive animal. It appears highly unlikely that this effect is caused by physical activity (see "Discussion").

ODP in adult dominant male mice is dependent on the activation of the serotonin receptor 5-HT_{1A}

It has already been shown that adult ODP can be restored by an increased serotonin transmission (Maya Vetencourt et al. 2008, 2011), and that the effects of enriched environment and social experience, which also induce ODP, are mediated by this transmitter (Baroncelli et al. 2010; Balog et al. 2014). We therefore wanted to check if serotonin plays a role for the reinstated plasticity of socially dominant mice. After the second optical imaging session, the mice were returned to their respective housing conditions for another 3 days, whereupon they were sacrificed for post-mortem HPLC. Figure 2a shows that the contents of serotonin (5-HT) and its metabolite 5-hydroxy-indole-acetic acid (5-HIAA) were not

different between dominant and submissive paired mice with running wheel (dominant 5-HT: 8.38 nmol/mg protein ± 1.38 vs. submissive 5-HT: 8.41 nmol/mg protein ± 1.83, $p = 1.0$; dominant 5-HIAA: 2.93 nmol/mg protein ± 0.65 vs. submissive 5-HIAA: 2.92 nmol/mg protein ± 0.84, $p = 1.0$, $n = 9$). 5-HT turnover (5-HIAA/5-HT ratio), too, was indistinguishable (dominant: 0.35 ± 0.03, submissive: 0.36 ± 0.05, $p = 1$, $n = 9$, data not shown). Data of cage mice and mice from an arena with running wheel were pooled for this analysis (see above). This result was surprising, as it effectively excludes serotonin as an inductor of ODP in our present model.

We therefore wondered whether it might at least be a permissive factor. To answer this question, we compared the contents of 5-HT and 5-HIAA in pooled dominant and submissive mice to both single-housed mice (which show no plasticity) and arena mice (which show serotonin-dependent plasticity, Balog et al. 2014). 5-HT and 5-HIAA contents (Fig. 2a) were highly variable in our hands and precluded any conclusion: Both single mice (5-HT: 6.2 ± 1.17 nmol/mg protein and 5-HIAA: 3.45 ± 0.79 nmol/mg protein, $n = 5$), and paired mice in an arena without a running wheel (5-HT: 8.32 ± 2.56 nmol/mg protein and 5-HIAA: 1.99 ± 0.49 nmol/mg protein, $n = 4$) showed similar values as caged pairs. However, the 5-HT turnover (5-HIAA/5-HT ratio) was significantly affected by housing condition ($F_{2,24} = 5.09$, $p \leq 0.05$, ANOVA), as it was lower in both pair-housed groups than in single-housed animals (single cage: 0.55 ± 0.1, $n = 5$, paired cage with rw: 0.35 ± 0.03, $n = 18$, $p \leq 0.05$, paired arena w/o rw: 0.26 ± 0.03, $n = 4$, $p \leq 0.05$, Tukey test). This finding suggests that 5-HT transmission is not sufficient to induce ODP in dominant male mice, but is necessary as a permissive factor.

To test this interpretation, we treated animals with WAY-100635, the antagonist of the 5-HT_{1A} receptor (Fig. 2c). We targeted this specific receptor because, on the one hand, it is crucially involved in the regulation of mood and social behaviour (Bell and Hobson 1994), and, on the other hand, it has been shown to principally mediate the effect of 5-HT on ODP (Maya Vetencourt et al. 2011; Balog et al. 2014; Gagolewicz and Dringenberg 2016). Indeed, this intervention inhibited ODP in dominant paired cage animals after 4 days of MD (0.23 ± 0.04–0.28 ± 0.03, $p = 0.6$, $n = 4$). ANOVA showed significant effects of social dominance ($F_{1,12} = 6.35$, $p \leq 0.05$), MD ($F_{1,12} = 17.752$, $p \leq 0.001$) and treatment ($F_{1,12} = 4.797$, $p \leq 0.005$), as well as all of their interactions (all $p \leq 0.01$). Post hoc Tukey testing revealed that the ODI did not change in the submissive paired cage animals during MD (0.23 ± 0.01–0.25 ± 0.04, $p = 1$, $n = 4$). In the saline control group, the ODI of the dominant paired cage control animals was significantly decreased after 4 days MD (0.24 ± 0.02 to − 0.01 ± 0.02, $p \leq 0.001$, $n = 4$). As expected, the ODI of the submissive paired cage mice did not change (0.28 ± 0.04–0.25 ± 0.03, $p = 0.9$, $n = 4$). These results confirm that 5-HT_{1A} receptor activation is required to mediate the enhanced ODP in adult dominant paired cage mice.

Analysis of the response amplitudes (Fig. 2d) confirmed that cortical activation by the contralateral eye remained significantly stronger than by the ipsilateral eye in all conditions where ODP was absent. Apart from the factor "eye" and its interactions with the other variables, no other factor had any effect on the amplitudes, according to ANOVA. The cortical responses to the ipsilateral and contralateral eyes were consistent in both dominant and submissive WAY-100635-treated animals before and after MD, with an apparent decrease in ipsilateral activity predominantly in the dominant animals explaining increased ODIs (dominant: contra before MD: $[2.41 \pm 0.39] \times 10^{-4}$ vs. contra after MD: $[2.32 \pm 0.44] \times 10^{-4}$, $p = 1$; ipsi before MD: $[1.63 \pm 0.21] \times 10^{-4}$ vs. ipsi after MD: $[1.33 \pm 0.24] \times 10^{-4}$, $p = 1$, $n = 4$; submissive: contra before MD: $[2.54 \pm 0.34] \times 10^{-4}$ vs. contra after MD: $[2.59 \pm 0.28] \times 10^{-4}$, $p = 1$, ipsi before MD: $[1.81 \pm 0.15] \times 10^{-4}$ vs. ipsi after MD: $[1.58 \pm 0.12] \times 10^{-4}$, $p = 1$, $n = 4$).

To our surprise, there was a significant decline in contralateral deprived-eye responses to open-eye levels in dominant vehicle animals (contra: $[3.36 \pm 0.57] \times 10^{-4}$ to $[2.5 \pm 0.48] \times 10^{-4}$, $p \leq 0.05$; ipsi: $[2.15 \pm 0.38] \times 10^{-4}$ to $[2.39 \pm 0.31] \times 10^{-4}$, $p = 0.1$, $n = 4$), which is typically considered the juvenile mode of plasticity, and contrasts with the adult plasticity—i.e., increase in open-eye responses—previously observed in untreated animals in the present study (Fig. 1f).

Taken together, reduced 5-HT turnover appears to be a necessary, permissive factor for the ODP observed in paired mice, but it does not cause the difference in plasticity between dominant and submissive animals.

ODP in socially dominant male mice is regulated by cortical inhibition and Hebbian plasticity

Restored ODP in fully adult mice is frequently associated with a decrease in cortical GABA release, and can be blocked by diazepam administration (Hanover et al. 1999; Harauzov et al. 2010; Huang et al. 1999; Maya Vetencourt et al. 2011; Sale et al. 2007). It has repeatedly been shown, too, that the initial phase of both juvenile and adult ODP consists of NMDA receptor-dependent Hebbian LTP and LTD (Sawtell et al. 2003; Sato and Stryker 2008; Ranson et al. 2012). To check whether the same plasticity mechanisms are at work in socially dominant male mice, we treated experimental groups of mice with either diazepam or the NMDA receptor blocker CPP.

Figure 3a shows that ODP in dominant paired cage mice was abolished by both interventions,

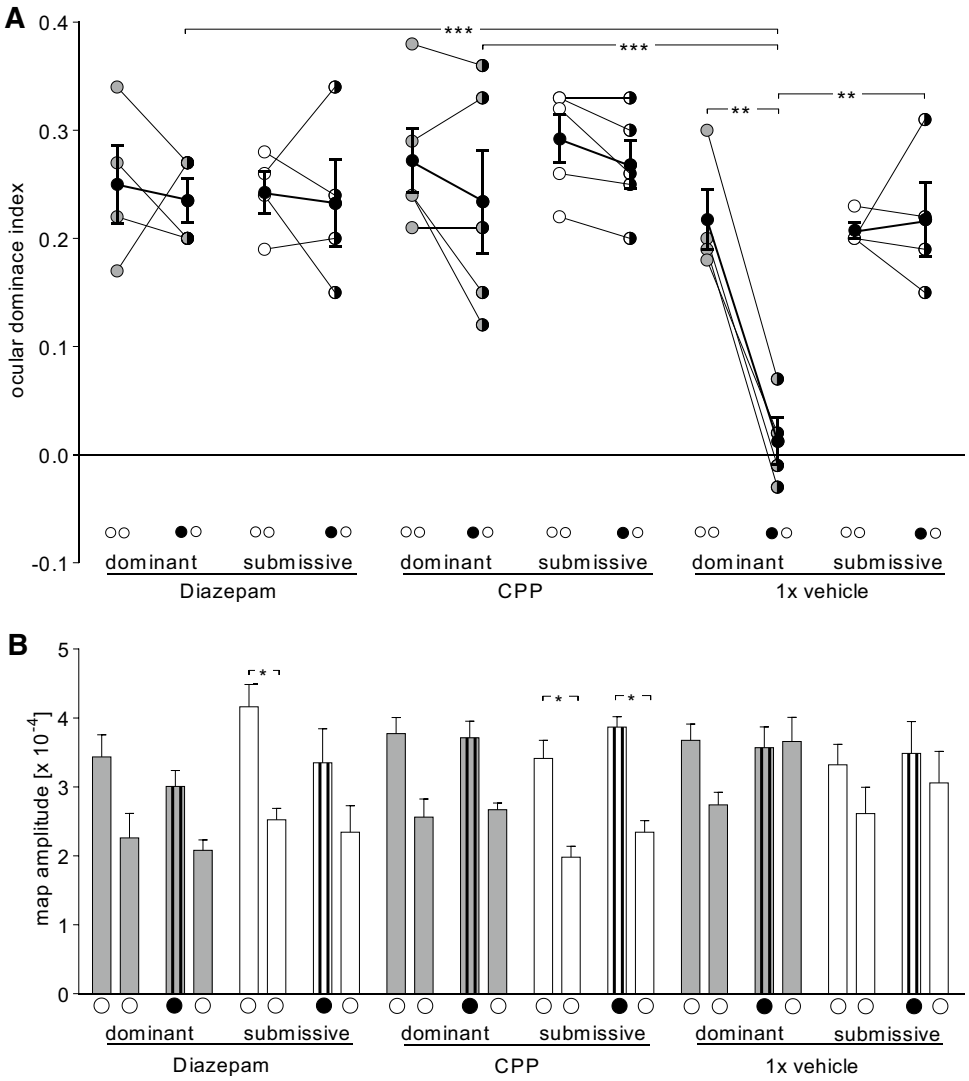

Fig. 3 Cortical inhibition and long-term potentiation are involved in social dominance-induced ODP. **a** Both diazepam ($p=1$, $n=4$) and CPP ($p=1$, $n=5$) blocked ODP in socially dominant male mice. Vehicle-treated dominant mice occur a significant shift towards the open eye ($p\leq0.01$, $n=4$). **b** Contralateral eye responses remained higher than ipsilateral eye responses in all treated groups, but there was an obvious increase of ipsilateral eye responses in dominant vehicle mice ($p\leq0.9$, $n=4$). All conventions are as in Fig. 1

diazepam (0.25 ± 0.04–0.24 ± 0.02, $p=1$, $n=4$) and CPP (0.27 ± 0.03–0.23 ± 0.05, $p=1$, $n=5$). As usual, the submissive paired cage animals did not show any ODP, neither under diazepam treatment (0.24 ± 0.02 vs. 0.23 ± 0.04, $n=4$, $p=1$, $n=4$), nor under CPP treatment (0.29 ± 0.02 vs. 0.27 ± 0.02, $n=5$, $p=1$, $n=5$). As the vehicle group was included into the ANOVA, there were significant effects of MD (diazepam: $F_{1.12}=11.084$, $p\leq0.001$, CPP: $F_{1.14}=31.116$, $p\leq0.001$) and treatment (diazepam: $F_{1.12}=11.64$, $p\leq0.01$; CPP: $F_{1.14}=15.628$, $p\leq0.001$) for both interventions, together with all interventions. By post hoc Tukey testing, these effects could be attributed to the fact that in the vehicle group, a strong OD shift was found in dominant paired cage animals (0.22 ± 0.03–0.01 ± 0.03, $n=4$, $p\leq0.01$, $n=4$), which made the values significantly different from those in the corresponding treatment groups ($p\leq0.001$ in both groups). This shift was here again due to an obvious, but not significant increase in open-eye responses (Fig. 3b, $[2.74\pm0.18]\times10^{-4}$ vs. $[3.66\pm0.35]\times10^{-4}$; $p\leq0.9$; Tukey test, $n=4$), whereas the response of the contralateral eyes stayed the same. The animals receiving vehicle once per day thus resemble untreated animals. The ODI of submissive control animals did not change after 4 days of MD.

In all diazepam-treated groups, V1 activity elicited by contra- or ipsilateral eye stimulation remained unchanged in dominant (contra: $[3.44\pm0.32]\times10^{-4}$ vs. $[3.01\pm0.23]\times10^{-4}$; $p=1$; ipsi: $[2.26\pm0.35]\times10^{-4}$ vs. $[2.08\pm0.15]\times10^{-4}$; $p=1$, $n=4$) and submissive animals (contra: $[4.16\pm0.32]\times10^{-4}$ vs. $[3.35\pm0.49]\times10^{-4}$; $p=1$; ipsi: $[2.52\pm0.17]\times10^{-4}$ vs. $[2.34\pm0.39]\times10^{-4}$; $p=1$, $n=4$, all analyses by post hoc Tukey test). The strength of the responses of contralateral and ipsilateral eyes also remained the same in the dominant and submissive CPP-treated animals after 4 days MD.

Thus, as in other paradigms that reinstate adult ODP, the OD shift in adult dominant mice is mediated by Hebbian plasticity and depends on reduced GABA transmission.

Social rank is independent from serotonin, GABA and NMDA transmission

During the administration of drugs that prevented ODP, running wheel use was monitored on a daily basis (Fig. 4). Although the drugs had some global effects on behaviour and, consequently, motivation to enter the running wheel, neither WAY-100635 (Fig. 4a) nor diazepam (Fig. 4b) nor CPP (Fig. 4c) changed the social hierarchy between the two mice of a pair.

As a serotonin antagonist, WAY-100635 predictably increased the aggression especially of the dominant mouse. In consequence, the dominant animal defended its access to the running wheel, whereas the submissive partner appeared even more subdued after the initiation of the WAY-100635 treatment. ANOVA confirmed an effect of dominance ($F_{1.12} = 15.937$, $p \leq 0.01$).

In contrast, both diazepam and CPP decreased running wheel use of dominant and submissive mice alike (repeated measures factor, diazepam: $F_{1.12} = 3.432$, $p = 0.089$; CPP: $F_{1.14} = 5.537$, $p \leq 0.05$, ANOVA), but social dominance remained the most influential factor (diazepam: $F_{1.12} = 21.948$, $p \leq 0.001$; CPP: $F_{1.14} = 12.656$, $p \leq 0.01$). Thus, when together, dominant mice kept running more than submissive ones in all treatment groups, with the latter turning the wheel more eagerly when alone.

These observations indicate that interference with serotonin, GABA or glutamate–NMDA transmission do not act on the social status to abolish ODP in dominant mice. Rather, they work independently from the neuronal representation of social hierarchy, presumably locally in the visual cortex.

Dopamine regulates social dominance and ODP of adult male mice

As the medial prefrontal cortex (mPFC) bidirectionally regulates the social status of mice (Wang et al. 2011), and can also exert an influence on V1 processing (Nguyen et al. 2015; Noudoost and Moore 2011), we wondered whether it might have the capacity to control ODP as well. Therefore, we first checked whether the visual cortex received input from the mPFC by performing retrograde tracing from anterior and posterior portions of the binocular visual cortex (Fig. 5a). Indeed, labelled neurons were found within deep layers in the anterior cingulate subregion of the mPFC in 3 out of 3 animals. It is interesting to note that these projections appear to be topographically arranged, with more ventrally situated neurons sending axons to more caudal subregions of the visual cortex.

Next, we determined the dopamine content in the mPFC by HPLC. In seven out of eight cases, the content was higher in the dominant than the submissive animal of a pair (Fig. 5b). On average, dominant mice had

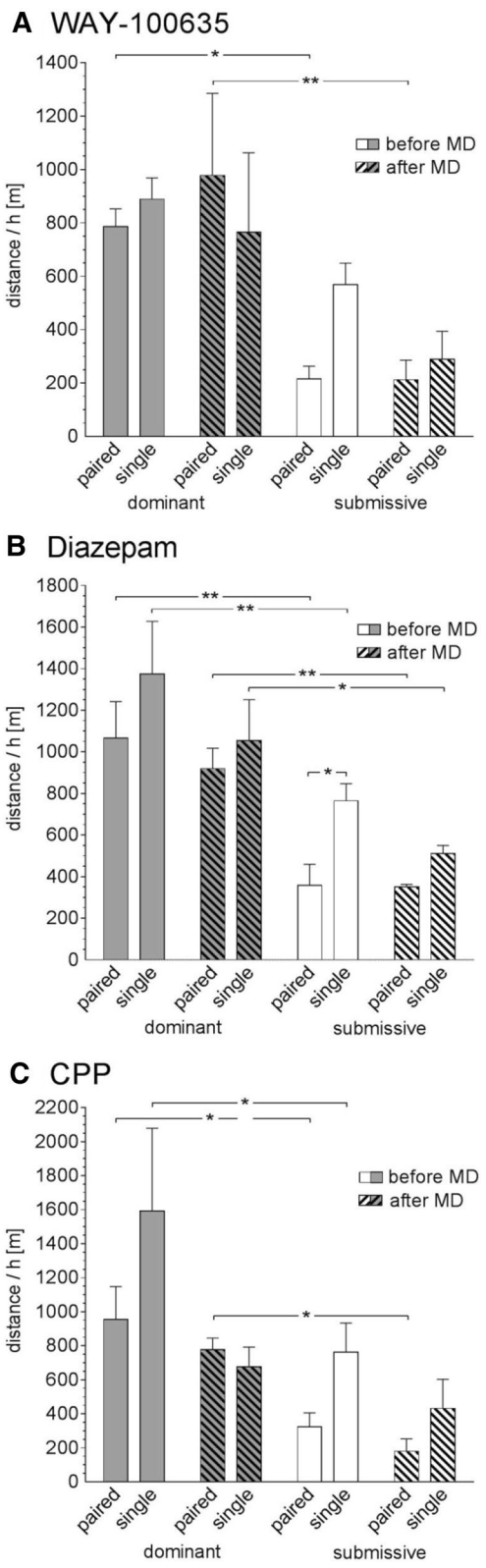

Fig. 4 Running wheel data under WAY-100635, diazepam and CPP treatment. Neither WAY-100635 ($n = 8$) (**a**) nor diazepam ($n = 8$) (**b**) nor CPP ($n = 10$) (**c**) changed the social hierarchy between the two mice of a pair

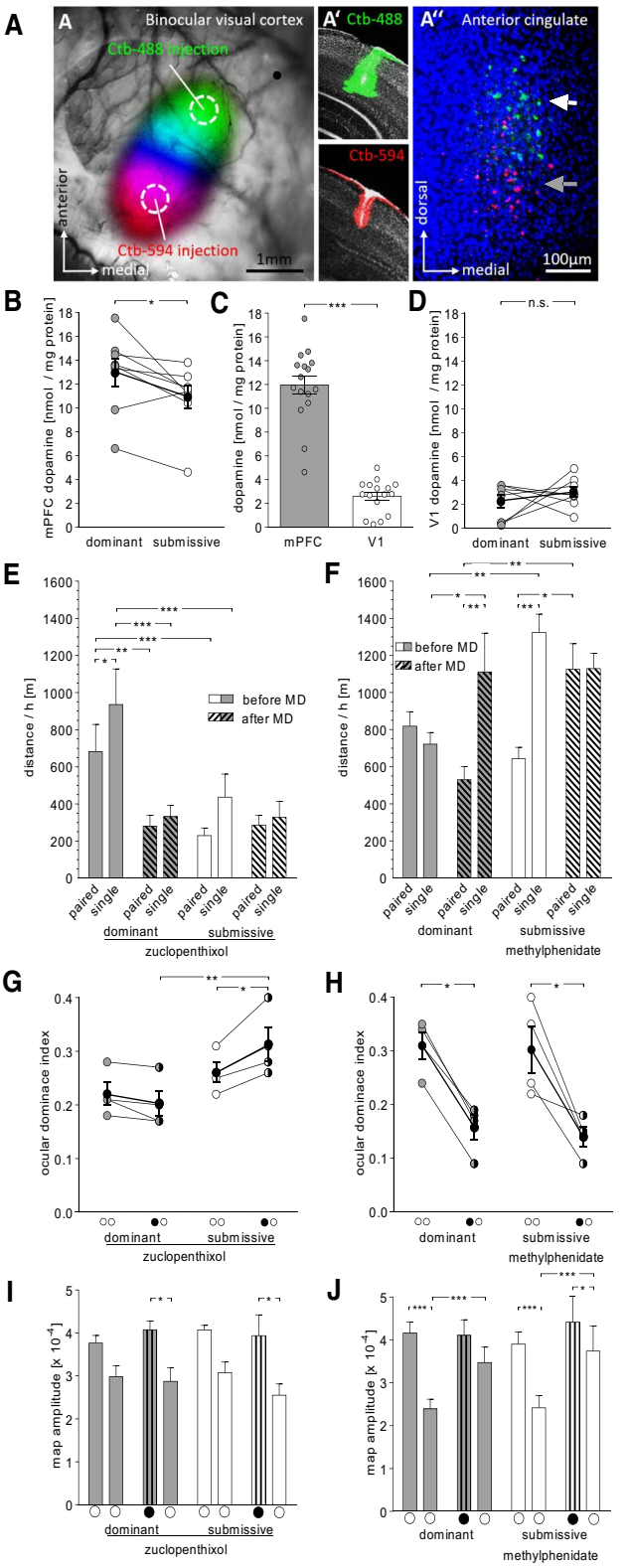

Fig. 5 Cortical dopamine transmission regulates ODP in mice. **a** By ▶ retrograde tracing of the visual cortex of ($n=3$), labelled neurons were found in the mPFC. Anterior parts of V1 (green, brighter in black and white reproductions) are innervated by more dorsal parts of the anterior cingulate (white arrow), more posterior parts (red, darker in b/w) by the more ventral anterior cingulate (grey arrow). **b** Dopamine content is higher in the mPFC of dominant than submissive ($p \leq 0.05$, $n=8$ vs. 8) animals. **c** Dopamine fibres are highly represented in higher-order cortices, but hardly present in sensory cortices. The dopamine content between mPFC and V1 of dominant and submissive mice (shown pooled) is highly significantly different ($p \leq 0.001$, $n=16$ vs. 16). **d** There was no difference in the dopamine content in V1 between dominant and submissive mice ($p=0.2$, $n=8$ vs. 8). **e** Zuclopenthixol treatment abolished the differential running wheel use of dominant and submissive mice ($n=8$). **f** The dominance relationship between the mice is partly reversed upon methylphenidate treatment ($n=8$). **g** The dopamine receptor antagonist zuclopenthixol blocked ODP of the dominant mice ($p=0.4$, $n=4$) and even increased the ODI of submissive mice ($p \leq 0.05$, $n=4$). **h** In contrast, the dopaminergic agonist methylphenidate, administered to the submissive animal, resulted in both animals displaying ODP (both: $p \leq 0.05$, $n=8$). **i**, **j** Cortical response amplitudes elicited by stimulation of the contralateral and ipsilateral eyes. Dominant and submissive methylphenidate-treated mice showed a strong significant increase in the open-eye response ($p \leq 0.001$, $n=8$)

12.96 ± 1.18 nmol/mg protein, and submissive mice had 10.93 ± 0.97 nmol/mg protein dopamine in the mPFC, a difference that proved to be significant ($p \leq 0.05$, $n=8$ vs. 8). As the rodent visual cortex receives next to no dopamine fibres (Berger et al. 1976), its dopamine content is accordingly vastly lower than in the mPFC ($p \leq 0.001$, $n=16$ vs. 16, Fig. 5c). Moreover, there was no difference between dominant and submissive mice in the visual cortex ($p=1$, $n=8$ vs. 8, Fig. 5d). Thus, mPFC dopamine might play a role in mediating between social dominance and ODP.

To check this assumption, we bidirectionally manipulated cortical dopamine transmission. To reduce it, we administered a low dose (0.2 mg/kg) of the neuroleptic zuclopenthixol. Zuclopenthixol blocks both D1 and D2 receptors, with little cross-action at other aminergic receptors. Moreover, the small dose is reported to reduce aggression, but to have no effect on motor behaviour, thus probably acting in the mPFC rather than the striatum (Manzaneque and Navarro 1999).

Indeed, this intervention not only reduced locomotion globally ($F_{1,6}=10.398$, $p \leq 0.05$, ANOVA)—as would be expected from a neuroleptic—but specifically abolished the differential running wheel use of dominant and submissive mice (Fig. 5e). According to two-factor ANOVA with repeated measures, there was no overall effect of social dominance ($F_{1,6}=3.993$, $p > 0.05$), but an interaction of social dominance with treatment ($F_{1,6}=8.439$, $p \leq 0.05$), which could be traced to significantly reduced running in dominant mice only after zuclopenthixol treatment, using post hoc testing (paired running: $p \leq 0.01$, $n=4$, single running: $p \leq 0.001$, $n=4$). Running activity in submissive mice, in contrast, was in no way influenced by the neuroleptic.

Accordingly, optical imaging of intrinsic signals showed that zuclopenthixol treatment blocked ODP of dominant

animals (Fig. 5g, 0.22 ± 0.02 vs. 0.20 ± 0.02, $p = 0.4$, $n = 4$), and even resulted in significant increased ODIs in submissive mice after 4 days MD (0.26 ± 0.02–0.31 ± 0.03, $p = 0.05$, $n = 4$). OD was not affected by either social rank ($F_{1.6} = 5.118$, $p > 0.05$) or MD ($F_{1.6} = 5.345$, $p > 0.05$), according to ANOVA, but there was an interaction ($F_{1.6} = 21.382$, $p \leq 0.01$), which was due to the increased ODI in submissive animals. In both dominant and submissive cage paired animals treated with zuclopenthixol, there was no change in amplitude data, as before and after MD the ocular dominance remained on the contralateral eye, but there is a tendency of decreased ipsilateral response in the submissive animals (Fig. 5i), which explains the increased ODIs. According to ANOVA, however, apart from the striking influence of eye, no other factor had a significant influence.

Finally, we systemically administrated the dopamine reuptake inhibitor methylphenidate hydrochloride to submissive paired arena mice. Here, we faced the problem that social status is a relative concept, such that there cannot logically be two (out of two) dominant mice. Indeed, preliminary experiments had shown that administration of the drug to mice confined to the narrow cage, as well as administration to both mice in the arena, resulted in escalating violence that could not be tolerated. We therefore resorted to the arena with running wheel paradigm established above, where it was possible for both mice to keep a distance. Here, we injected only the submissive mouse with a low dose of methylphenidate that has been shown to increase mPFC, but not striatal dopamine (Koda et al. 2010).

The dominance relationship between the mice indeed became more ambiguous, appearing partly reversed, upon this treatment (Fig. 5f). The methylphenidate-treated submissive mice increased their wheel use at the expense of the dominant partners, who, in turn, resorted to more vigorous running when alone. While this pattern suggests a complete reversal of social hierarchy, behavioural observation showed a lot of agonistic behaviour and competition for the wheel that is more in line with the notion that the rank question remained unsettled during the treatment.

Remarkably, methylphenidate treatment of the submissive mouse indeed resulted in ODP in both the originally dominant and the submissive mouse (Fig. 5h). As expected, the untreated dominant mice showed a shift of the ocular dominance towards the open, ipsilateral eye (0.31 ± 0.03–0.16 ± 0.02, $p \leq 0.05$, $n = 4$). Amazingly, the methylphenidate-treated submissive mice also did show an OD shift of similar magnitude (0.30 ± 0.04–0.14 ± 0.02, $p \leq 0.05$, $n = 4$). Thus, whereas MD had a highly significant influence on the data ($F_{1.6} = 39.758$, $p \leq 0.001$), social dominance had none ($F_{1.6} = 0.115$, $p > 0.5$), and the shifts were significant in both groups, according to post hoc Tukey tests. Although the OD shift did not lead to a balanced ODI of 0 in the open-field paired mice, a significant increase in responsiveness from the open eye was found after MD in dominant and in submissive animals (dominant: contra: $[4.16 \pm 0.26] \times 10^{-4}$ vs. $[4.11 \pm 0.36] \times 10^{-4}$, $p = 1$, ipsi: $[2.39 \pm 0.22] \times 10^{-4}$ vs. $[3.47 \pm 0.36] \times 10^{-4}$, $p \leq 0.001$; submissive: contra: $[3.9 \pm 0.28] \times 10^{-4}$ vs. $[4.42 \pm 0.68] \times 10^{-4}$, $p = 1$; ipsi: $[2.42 \pm 0.28] \times 10^{-4}$ vs. $[3.74 \pm 0.58] \times 10^{-4}$; $p \leq 0.001$, $n = 8$, all comparisons with Tukey test, Fig. 5j), although there was a significant interaction of MD and eye ($F_{1.6} = 48.148$, $p \leq 0.001$, ANOVA).

Thus, dopamine metabolism in the mPFC is influenced by social status and could influence the visual cortex via direct connections. Systemically applied drugs that manipulate dopamine transmission indeed change ODP in the expected direction, with an agonist inducing and an antagonist blocking it.

Thus, it could be confirmed that a bidirectional manipulation of the dopamine transmission in the mPFC can change the social status, the behaviour and also the ODP in the V1, by a direct connection of both cortices, of adult male mice.

Discussion

In this paper, we have shown the connection between social dominance status and ODP: while ODP can be observed in either mouse if two animals are housed together in a large arena (Balog et al. 2014), constraining the space or introducing a limited resource (running wheel) abolishes ODP in the submissive animal.

Methodological considerations

We have based our assessment of relative social status mostly on the differential use of the running wheel. Observations of agonistic behaviour and physical appearance corroborated our judgement by this new measure, which was introduced for pragmatic reasons: Adult male mice that tolerate each other for a sufficient period of time to induce ODP (i.e., at least 4 days) show very little agonistic behaviour to rely on (Balog et al. 2014). Even preliminary attempts to use a variant of the tube test (Malatynska et al. 2002) failed to yield conclusive results. A running wheel, however, has been shown to be a highly attractive feature for mice (Meijer and Robbers 2014). By comparing its use when mice were together and when alone, we could make sure that lesser use in one animal was not due to lack of interest. In addition, this procedure provided the submissive mouse with some running time. Although we have previously conclusively shown that wheel running over only a few days of monocular deprivation (MD) is ineffective in inducing ODP in adult mice (Balog et al. 2014), this arrangement makes such a causation additionally unlikely in the present study.

Nonetheless, another group (Kalogeraki et al. 2014, 2016, 2017) has repeatedly claimed to have induced ODP in fully adult male mice by providing access to a running wheel during 7 days of MD. There are, however, fundamental differences in study design that probably explain the discrepancy. First, in those studies, the mice were apparently (Kalogeraki et al. 2014) or explicitly (Kalogeraki et al. 2016, 2017) housed socially (three to five mice per cage). We have shown that social housing induced ODP (Balog et al. 2014), but a control group of socially housed animals without running wheel is lacking in the conflicting studies. Second, they used 7 days of MD, whereas we used 4 days, which is the standard duration to check for critical period—like plasticity (Gordon and Stryker 1996). Third, in the conflicting studies, mice had constant access to the running wheel for 24 h a day, and the only single-housed experimental group had constant access to a running wheel for 14 days (Kalogeraki et al. 2016). Other researchers have confirmed that short-term (4 h/day) running only reinstates ODP in adult mice if accompanied by strong visual stimulation (Kaneko and Stryker 2014). Indeed, longer (6 h/day) visual stimulation can increase ODP by itself (Matthies et al. 2013).

In our previous study, we have shown that providing single-housed mice with a running wheel throughout 4 days of MD failed to induce ODP (Balog et al. 2014). We here substantiate this observation by finding no correlation between running distance and plasticity in neither dominant nor submissive mice. Still, one might argue that single housing is stressful for mice, thus blocking ODP, and that in the correlation data, there is little overlap between the running distances of dominant and submissive mice, still allowing for running to play a role. As for the first point, an involvement of stress in the regulation of socially modulated plasticity is probable and highly interesting (Spolidoro et al. 2011). Studies in pairs of mice have shown that the ability to learn (Fitchett et al. 2005; Colas-Zelin et al. 2012; Matzel et al. 2017) as well as synaptic plasticity (Wang et al. 2016) actually degrade in submissive animals, which have an elevated basal corticosterone level (Blanchard et al. 1995; McKittrick et al. 1995, 2000). Thus, stress is possibly involved as a mediating, but not alternative factor in blocking ODP in submissive mice. Concerning the second objection, it is conceivable, but highly unlikely that there should be an on/off switch for ODP at 2100 m/day that we have hit upon by pure chance.

Finally and possibly most crucially, as stated in the introduction, the differing ODP among two male mice housed together in a standard cage was already observed in our first study—sparking the investigation presented here—although no running wheel was present. Thus, we can safely exclude that our method to assess social dominance could in any way interfere with ODP.

ODP was Hebbian and required attenuated GABA and increased serotonin transmission

Ocular dominance plasticity in dominant mice was shown to be Hebbian in the present study, as it was blocked by the NMDA antagonist CPP, thus confirming the current knowledge on the early phase of ODP (Sawtell et al. 2003; Sato and Stryker 2008; Ranson et al. 2012). Furthermore, it required reduced GABA inhibition and increased serotonin transmission. This, too, is in line with a host of studies (Sale et al. 2007; Maya Vetencourt et al. 2008, 2011; Spolidoro et al. 2009; Harauzov et al. 2010). In addition, serotonin is strongly involved in the regulation of social behaviour, and its release is altered by housing conditions (Miura et al. 2008).

In our study, however, serotonin concentrations and turnover did not distinguish between dominant and submissive mice, suggesting that social housing induces changes in serotonin metabolism which are necessary, but not sufficient, for adult ODP (Balog et al. 2014). The experience of being submissive—elicited here by presentation of a running wheel—then secondarily blocks plasticity by another, non-serotonin-dependent mechanism. In line with this reasoning, the treatments of diazepam, WAY-100635 and CPP did not affect the dominant and submissive behaviour of the mice. Thus, ODP mediated by social status can be regulated by brain structures outside of the visual cortex.

Higher-order cortices are involved in regulating adult ODP

In line with this reasoning, we have shown that manipulation of dopamine transmission, using dopaminergic drugs at concentrations that have no effects in the striatum, but in the PFC (Manzaneque and Navarro 1999; Koda et al. 2010), bidirectionally regulated ODP. Dopamine afferents are only received by higher-order cortices, but spare the primary sensory cortices (Berger et al. 1976; Kalsbeek et al. 1987). Thus, this observation proves that plasticity in a primary sensory cortex is controlled by higher-order cortices, most likely the medial PFC (mPFC), which is a key structure for cognition, mental health, and social behaviour (Wang et al. 2011, 2014; Wass et al. 2018). Social status is bidirectionally regulated by the mPFC (Wang et al. 2011), and mPFC neurons are active during social interactions which clarify the social rank (Murugan et al. 2017; Liang et al. 2018). A recent study has even demonstrated a correlation of dorsomedial PFC neurons' activity across pairs of mice, which is mostly driven by the dominant partner (Kingsbury et al. 2019). In rodents, the PFC receives an exclusive projection of dopamine fibres from the ventral tegmentum, which are prominently involved in its functioning (Winterfeld et al. 1998; Wass et al. 2018), including the establishment

of social hierarchy (Yamaguchi et al. 2017). By its efferents, the mPFC can exert widespread influences on brain functions. Amongst others, it has direct connections to the visual cortex (Sesack et al. 1989; Zhang et al. 2016), which we have confirmed in the present study and shown to be topographic in nature. By these connections, the mPFC can regulate sensory processing and attention in the visual cortex (Zhang et al. 2014; Nguyen et al. 2015; Noudoost and Moore, 2011).

In accordance with these studies, we have shown in the present study that dopamine content in the mPFC was higher in dominant than submissive animals. Using both a specific agonist and antagonist, we could further demonstrate that the dominance behaviour of the mice is bidirectionally altered by dopamine transmission, resulting in corresponding changes in the ODP within the primary visual cortex. The fact that, unlike serotonergic, GABAergic or glutamatergic interventions described above, dopaminergic interventions interfered not only with ODP, but also with the behavioural expression of social status, strongly argues for a causal link between these phenomena. I.e., whereas certain levels of serotonergic and GABAergic transmission are merely permissive for adult ODP, a certain level of dopaminergic transmission in the mPFC is necessary.

It remains an open question how the mPFC exerts its influence on V1 plasticity. Although there is a prominent projection from the mPFC to the dorsal raphe nuclei (Sesack et al. 1989; Peyron et al. 1998; Vázquez-Borsetti et al. 2009), we can exclude this route, as serotonin content and turnover were similar in dominant and submissive mice. As discussed above, the stress response may play a role. However, we rather favour a direct cortico-cortical connection, the existence of which is established (Sesack et al. 1989; Zhang et al. 2016), has been confirmed in the present study, and is known to regulate visual attention (Noudoost and Moore 2011). This suggestion can be further substantiated by other studies that have already shown that other cortical areas also affect processing and plasticity in the primary visual cortex (Teichert and Bolz 2017; Teichert et al. 2018a, b, c).

Additional observations

It was surprising that, while the ODI shift in dominant animals was uniform in all control groups, the underlying mechanism differed markedly: in untreated animals and animals with a single daily vehicle injection, it was achieved by an increase of ipsilateral response (so-called adult plasticity, Ranson et al. 2012; Sato and Stryker 2008). If mice received two daily vehicle injections, however, a decrease of the contralateral eye response was observed—so-called juvenile plasticity. This indicates that the brain can switch rather easily between these two modes of plasticity, both of which are basically Hebbian and appear to be distinguished only by the sliding threshold between long-term depression and potentiation (Philpot et al. 2003). In the present case, the switch might have been effected by the different stress levels caused by the injection regime. In line with these considerations, small differences in the housing procedure might also explain why we here observed adult plasticity in untreated arena mice (unrelated, group housed males) without running wheel, but documented juvenile plasticity in our previous study (previously isolated brothers, Balog et al. 2014).

Conclusion

We have shown in this study that ODP in adult male mice is dependent on social status. We have made a strong case for the assumption that the mPFC, which represents the social status, is on the one hand influenced by dopamine transmission to organize submissive or dominant patterns of behaviour, and on the other hand suppresses ODP in the visual cortex of submissive animals, probably via a direct projection. The idea that associative cortices might regulate plasticity in the primary cortices has been uttered before (He et al. 2006, 2007; Lehmann 2010), but has, to our knowledge, never as yet been experimentally tested. Future studies using local application of drugs and optogenetic manipulations could show how this influence is mediated on a functional level.

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Compliance with ethical standards

Conflict of interest The authors are not aware of any competing interests that could compromise their research or its presentation.

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