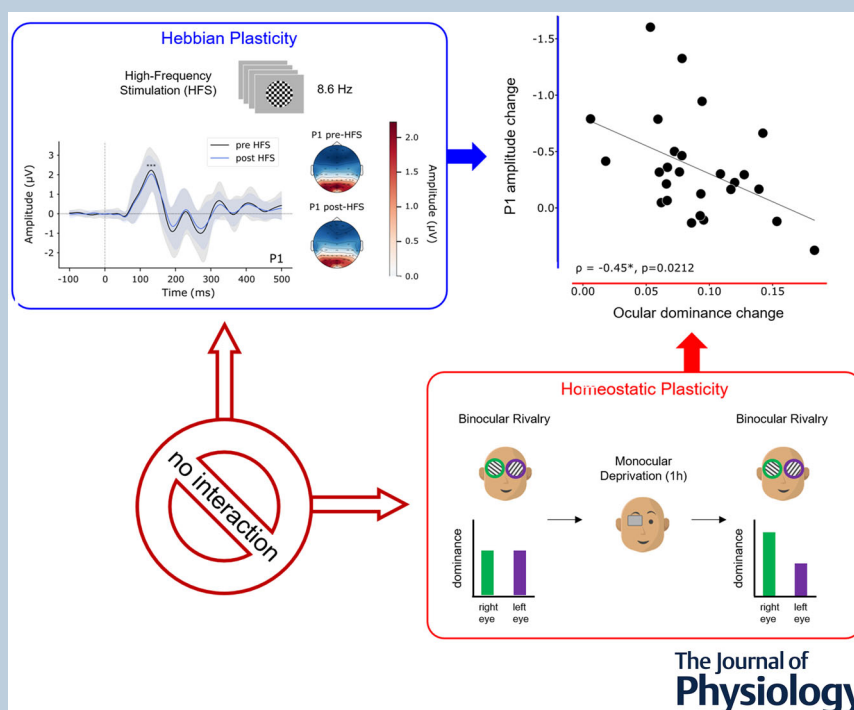# The interplay between Hebbian and homeostatic plasticity in the adult visual cortex

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Abstract figure legend (A) Modulation of the P1 component of visual evoked potential (VEP) by high-frequency stimulation (HFS) used as a proxy of Hebbian plasticity in adult humans. (B) Correlation between Hebbian and homeostatic plasticity across participants. (C) Boost of the deprived eye perceptual dominance measured with binocular rivalry after 1 h of monocular deprivation used as a proxy of homeostatic plasticity in adult humans.

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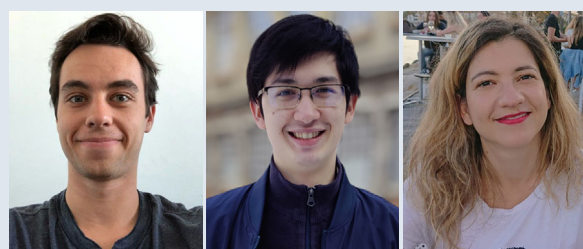
Abstract Homeostatic and Hebbian plasticity co-operate during the critical period, refining neuronal circuits; however, the interaction between these two forms of plasticity is still unclear, especially in adulthood. Here, we directly investigate this issue in adult humans using two consolidated paradigms to elicit each form of plasticity in the visual cortex: the long-term potentiation-like change of the visual evoked potential (VEP) induced by high-frequency stimulation (HFS) and the shift of ocular dominance induced by short-term monocular deprivation (MD). We tested homeostatic and Hebbian plasticity independently, then explored how they interacted by inducing them simultaneously in a group of adult healthy volunteers. We successfully induced both forms of plasticity: 60 min of MD induced a reliable change in ocular dominance and HFS reliably modulated the amplitude of the P1 component of the VEP. Importantly, we found that, across participants, homeostatic and Hebbian plasticity were negatively correlated, indicating related neural mechanisms, potentially linked to intracortical excitation/inhibition balance. On the other hand, we did not find an interaction when the two forms of plasticity were induced simultaneously. Our results indicate a largely preserved plastic potential in the visual cortex of the adult brain, for both short-term homeostatic and Hebbian plasticity. Crucially, we show for the first time a direct relationship between these two forms of plasticity in the adult human visual cortex, which could inform future research and treatment protocols for neurological diseases.

Key points

- Homeostatic and Hebbian plasticity co-operate during the critical period to refine neuronal circuits in the visual cortex.
- The interaction between these two forms of plasticity is still unknown, especially after the closure of the critical periods and in humans.
- We directly investigate the interplay between Hebbian and homeostatic visual plasticity in adult humans using non-invasive paradigms.
- We found a negative correlation between these forms of plasticity showing for the first time a direct relationship between Hebbian and homeostatic plasticity.
- Our results could inform future research and treatment protocols for neurological diseases.

Introduction

Neuroplasticity, the ability of the brain to undergo structural and functional changes in response to environmental and physiological stimuli, is a fundamental property of the central nervous system and plays a crucial role in the visual system's capacity for adaptation and learning (Pascual-Leone et al., 2005). During development, neuroplasticity is at its maximum and it is essential to refine and calibrate sensory systems based on the experience of the external environment (Berardi et al., 2015; Kolb et al., 2013; Takesian & Hensch, 2013). Sensory neuroplasticity has been extensively investigated in the visual system, where, during a specific temporal window occurring early on during development (called the critical period [Berardi et al., 2000; Hubel & Wiesel, 1970]), cortical organization [e.g.

ocular dominance (OD) (Blakemore & Van Sluyters, 1974; Hubel & Wiesel, 1977; Wiesel & Hubel, 1963) and orientation tuning (Bonds, 1979; Thompson et al., 1983)] is sculptured by visual experience, allowing the visual system to adapt to the external environment (Berardi et al., 2000; Hensch, 2004). After the closure of the critical period however, neuroplasticity drastically declines, and the visual cortex becomes more hard-wired (Blakemore, 1988; Espinosa & Stryker, 2012; Fuchs & Flügge, 2014; Morishita & Hensch, 2008; Wandell & Smirnakis, 2009). This decline in plasticity reduces the potential of the brain to recover from injury or conditions established during development, limiting the efficiency of neuro-rehabilitation in adulthood; for example, in the case of amblyopia (Fronius et al., 2014) or vision loss (Fine et al., 2003; Merabet & Pascual-Leone, 2010). Understanding the neural mechanisms underlying residual

visual plasticity past the critical period is therefore crucial for the development of new therapeutic strategies aimed at re-activating plasticity for visual rehabilitation.

Throughout life, two distinct yet complementary forms of neuroplasticity, Hebbian plasticity and homeostatic plasticity, work in tandem to maintain the stability and efficient functioning of neural circuits (Bang et al., 2023; Keck et al., 2017). Hebbian plasticity is characterized by the strengthening of synaptic connections between coactivated neurons (Hebb, 1949; Huang et al., 2014). Two canonical forms of Hebbian plasticity are long-term potentiation (LTP) and long-term depression (LTD), which induce long-lasting changes in the connection between neurons after repetitive concurrent stimulation (Malenka & Bear, 2004). LTP in particular has been proposed as one of the mechanisms underlying memory and learning (Bliss & Collingridge, 1993; Cooke & Bliss, 2006) and can be easily induced by direct electrical stimulation (Bliss & Lømo, 1973; Bliss & Collingridge, 1993). In the visual system, LTP and LTD mediate the long-term changes in the response properties of neurons driven by experience (Kilborn et al., 1996), with one paradigmatic example being that of OD plasticity, the dramatic shift of neuronal responses in favour of the open eye observed after long-term (weeks to months) monocular deprivation (MD) during development (Blakemore & Van Sluyters, 1974; Frenkel & Bear, 2004; Hensch & Quinlan, 2018; Holmes & Clarke, 2006; Hubel & Wiesel, 1964, 1970, 1977). In the framework of OD plasticity, LTP reinforces the connections between the non-deprived eye and the cortex, whereas LTD removes those from the deprived eye (Cooke & Bear, 2014). Homeostatic plasticity acts instead as a stabilizing mechanism, adjusting the overall excitability of neurons and synaptic strength to prevent runaway potentiation or depression and maintain neuronal firing rates within an optimal range (Mrsic-Flogel et al., 2007; Turrigiano & Nelson, 2004; Turrigiano, 2011, 2012). During development, homeostatic plasticity provides a crucial balance to the LTP and LTD mechanisms described above by regulating the neuronal firing rates around a sustainable level: left unchecked, LTP and LTD would drive any system to a runaway activity or to complete silence (Turrigiano & Nelson, 2004). In the context of OD plasticity, homeostatic plasticity has been linked to the increase in the deprived eye response after short-term MD, which occurs before the Hebbian potentiation of the non-deprived eye (Kaneko & Stryker, 2017; Turrigiano, 2017).

These two forms of plasticity are known to co-exist in the visual cortex (an introductory review is provided in Fox & Stryker, 2017), but very little is known about how they interact and work together, and their direct interaction has, to our knowledge, never been tested experimentally in adult humans.

In recent years, non-invasive approaches have been developed to investigate and characterize these two types of plasticity in adult humans. A form of visual homeostatic plasticity has been revealed in the framework of OD plasticity: after a few hours of MD, OD counter-intuitively shifts in favour of the deprived eye (Lunghi et al., 2011, 2013; Zhou et al., 2013) (for a review, see Baroncelli & Lunghi, 2021; Castaldi et al., 2020), indicating residual visual homeostatic plasticity after the critical period, mediated by a transitory up-regulation of contrast gain control mechanisms (Begum & Tso, 2016; Binda et al., 2018; Chadnova et al., 2017; Lunghi, Emir, et al., 2015; Lunghi, Berchicci, et al., 2015; Zhou et al., 2015). This shift in OD has been observed both at the perceptual [as measured mainly by binocular rivalry (Bai et al., 2017; Lunghi et al., 2013; Nguyen et al., 2021; Prosper et al., 2023; Steinwurzel et al., 2020) and binocular combination (Prosper et al., 2023; Tao et al., 2022; Wang et al., 2019; Zhou et al., 2013, 2014)] and at the neural level [as measured by a boost of the deprived eye responses through EEG (Lunghi, Berchicci, et al., 2015), functional magnetic resonance imaging (fMRI) (Binda et al., 2018) and magneto-encephalography (Chadnova et al., 2017))] and it is crucially mediated by a decrease in GABAergic inhibition in the primary visual cortex (Lunghi, Emir, et al., 2015). Several studies have investigated the multifaceted nature of this form of homeostatic plasticity, including its time course over the duration of deprivation (Min et al., 2018, 2022; Prosper et al., 2023) and its modulation by both visual [chromaticity (Lunghi et al., 2013), luminance (Yao et al., 2017; Zhou, Reynaud, Kim, et al., 2017), spatial frequency (Wang et al., 2019)] and non-visual [energy metabolism (Animali et al., 2023; Daniele et al., 2021; Lunghi, Daniele, et al., 2019), physical exercise (Lunghi & Sale, 2015; Lunghi, Sframeli, et al., 2019; Virathone et al., 2021; Zhou, Reynaud, Hess, et al., 2017), pharmacological manipulations (Sheynin et al., 2019), attention (Song et al., 2023; Wang et al., 2021), other forms of plasticity (Lo Verde et al., 2017; Sarı & Lunghi, 2023) and sleep (Menicucci et al., 2022)] factors. The paradigm of short-term MD is now established to probe the plastic potential of the visual cortex in typical and clinical populations (Lunghi et al., 2016; Lunghi, Sframeli, et al., 2019; Lunghi, Galli-Resta, et al., 2019; Lunghi, Daniele, et al., 2019; Min et al., 2022; Nguyen et al., 2023; Zhou et al., 2019) (for a review, see Baroncelli & Lunghi, 2021).

In parallel, a form of LTP/LTD-like Hebbian plasticity can be probed in the adult human visual cortex by measuring the modulation of the visual evoked potentials (VEPs) amplitude, after high-frequency visual stimulation (simulating the electric tetanus usually delivered to induce LTP/LTD in animal models) (for a review see, Sumner et al., 2020). This paradigm was inspired by animal studies

where non-invasive high-frequency visual stimulation was found to induce LTP-like changes in the neuronal connections of the visual system similar to direct, very high frequency cellular stimulation (Clapp et al., 2006; Sumner et al., 2020). Numerous studies have since employed this paradigm, or variations of it, providing mixed results: some studies reporting an increase in amplitude (McNair et al., 2006; Spriggs et al., 2018; Teyler et al., 2005), others showing a decrease in amplitude (Abuleil et al., 2019; Forsyth et al., 2015), and some studies describing substantial inter-individual variability and sometimes unreliable effects (Lahr et al., 2014; Sanders et al., 2018). Despite the lack of consensus around the direction of the effect of high-frequency stimulation (HFS) on the amplitude of VEPs, there is agreement on the Hebbian nature of this effect, which shows stimulus specificity (McNair et al., 2006; Ross et al., 2008) and NMDA receptor dependence (Çavuş et al., 2012; Cooke & Bear, 2014), two defining properties of Hebbian plasticity (Abbott & Nelson, 2000). Historically, two components of the VEP have been mainly investigated by studies using this paradigm: the P1 (also called P100) and the N1b component (Sumner et al., 2020). The P1 component is a positive voltage peak occurring around the occipital areas of the brain between 100 and 150 ms after stimulus presentation and originates from early visual areas such as V3, V3a and areas anterior to V4, but crucially not V1 (Di Russo et al., 2002; Di Russo, 2003). The N1b component is a bilateral negative component occurring around the parieto-occipital areas between 180 and 250 ms after stimulus presentation, it is defined in relation to the N1 and P2 components (for more details, see Methods) and involves activity in extra-striate areas such as V2 and the ventral part of V4 (Di Russo et al., 2002; Teyler et al., 2005).

Here, we use these two established paradigms to probe short-term homeostatic and Hebbian plasticity in adult humans, either independently or at the same time with the ultimate aim to elucidate the balance and relationship between these two complementary types of plasticity in the adult visual cortex.

Methods

Participants

Thirty-four participants were recruited for the study. Eight participants were excluded from the final sample for different reasons: two participants could not complete data collection because of scheduling constraints, two participants showed abnormalities in the EEG signal preventing us from extracting evoked responses [one of them showed a fully lateralized response with no activity in their left hemisphere, and their right hemisphere activity around one order of magnitude stronger than the other

participants (∼12 μV P1, compared to an average of 3–4 μV) (Fig. 1*C*), whereas the other participant showed a constant level of alpha waves (8–12 Hz) so dominant that we could not find reproducible peaks time-locked to our stimulus using our processing pipeline described below], one participant had very unstable OD at baseline (variations in baseline stronger than the effect of the MD procedure), the EEG data for one participant were corrupted and could not be recovered or recorded again and two participants were diagnosed with either psychiatric or neurological disorders halfway through the data collection.

The final sample therefore consisted of 26 adult participants (17 females, mean ± SD age 24.3 ± 2.4 years) including investigators AP and TB. All had normal or corrected to normal visual acuity (measured with ETDRS charts), had balanced OD at baseline (OD index <0.6) (for details on the computation of this index, see the section on Ocular dominance measurement), had no history of vision-related, psychiatric or neurological disorders, and, except for investigators AP and TB, all were naïve to the purpose of the experiment.

Ethical statement

The experiments were carried out under the French 'Comité de Protection des Personnes' ethical agreement RIPH2 no. 2022-A00963-40, with the support of the study given by the French 'Centre National de la Recherche Scientifique (CNRS)'. The study was performed in accordance with the Declaration of Helsinki (DoH-Oct2013) with the exception of registration in a database. All participants provided their written informed consent, and naïve participants were reimbursed for their time at a rate of €10 per hour for binocular rivalry sessions and €15 per hour for the EEG sessions.

Apparatus and stimuli

Binocular rivalry. Binocular rivalry measurements were performed in a dark and quiet room using a custom-built mirror stereoscope. Stimuli were presented on a 24 inch LCD monitor (XL2420Z; BenQ, Taipei, Taiwan) with a a maximum refresh rate of 144 Hz and a resolution of 1920 × 1080 pixels. The screen's luminance profile was gamma-corrected using a Minolta CS100A photometer (Konica Minolta Inc., Tokyo, Japan).

The stimuli were generated and presented using MATLAB, R2023b (The MathWorks Inc., Natick, MA, USA) and Psychtoolbox-3 (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997) on a Windows 11 PC (Alienware Aurora R8; Alienware Corporation, Miami, FL, USA) with a NVIDIA GeForce RTX 2080 graphics card (Nvidia Corporation, Santa Clara, CA, USA).

Participants rested their heads on a forehead and chin rest, with an optical path of 57 cm between their eyes and the screen. Responses were collected through continuous keyboard presses recorded every 100 ms.

The stimuli consisted of two sinusoidal gratings [orientation: $\pm45°$, spatial frequency: three cycles per degree (cpd), contrast: 64%] presented centrally in a circular window (diameter: 2°) on a uniform grey background (luminance: 110 cd m^{-2}, CIE: $x = 0.305$, $y = 0.332$). A red fixation cross was placed at the centre, surrounded by a white square frame (5° × 5°) containing complementary rectangles for each eye to facilitate dichoptic fusion (Fig. 2*A*). The dominant eye (defined as the eye showing the most dominance in the initial binocular rivalry measurement used for inclusion, after training) was patched for 60 min. The eye patch was custom-built from translucent plastic, allowing light (with 15% attenuation) but not patterns to reach the retina (Lunghi et al., 2013). Participants stayed in the laboratory during deprivation, where they were free to perform their regular activities (e.g. reading, working, walking around). MD was performed either in the morning or the afternoon, after participants had eaten breakfast or lunch, and the timing of all sessions was matched among participants to avoid metabolic confounds (Animali et al., 2023; Menicucci et al., 2022).

VEPs. VEPs were recorded in a dark, sound-proof, electrically insulated room using a Biosemi ActiveTwo 64-channels Ag/AgCl EEG system (Biosemi B.V., Amsterdam, The Netherlands) (sampling rate = 2 kHz). Because the potentials that we were investigating were reported along the parietal, parietal-occipital and occipital electrode lines of the 10–20 system (Di Russo et al., 2002; Sumner et al., 2020; Teyler et al., 2005), we chose a custom 33-channel subset of the 10–20 configuration, with denser electrode placement along the parietal, parietal-occipital and occipital lines of the 10–20 configuration. Two additional electrodes were placed on the mastoid to record movement artifacts for offline artifact correction, for a total of 35 channels recorded (Fig. 1*B*).
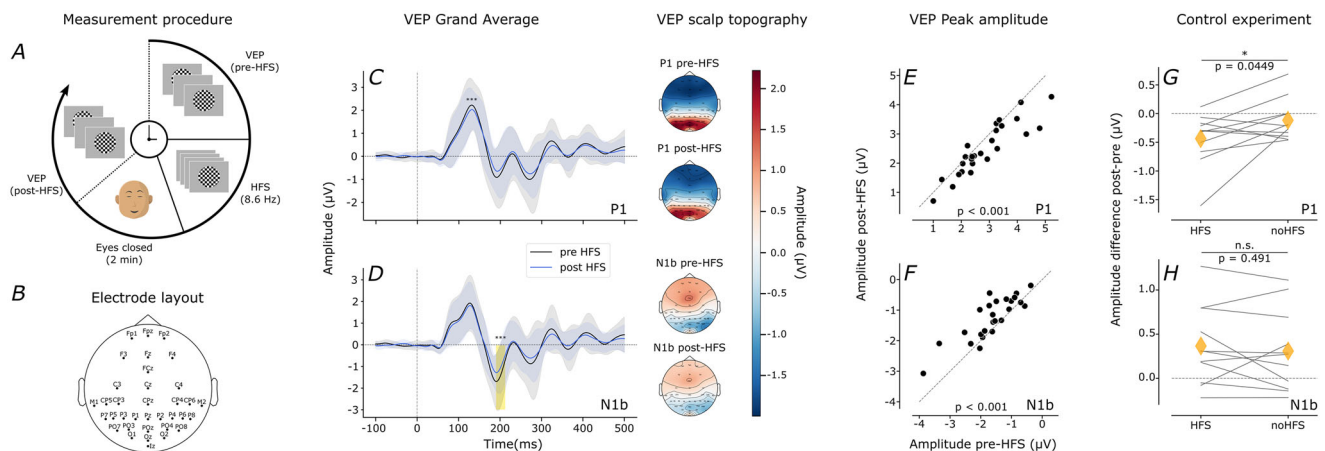

Figure 1. Experimental design and results: Hebbian plasticity paradigm

A, experimental paradigm timeline. Visual evoked potentials (VEPs) were measured in response to 500 stimulus presentations (presentation frequency: 0.8 Hz, SOA: 600–1500 ms) before the high-frequency stimulation (HFS) block composed of 1000 checkerboards at a rate of 8.6 Hz (SOA: 67–100 ms). VEPs were measured again after HFS and after a resting period of 2 min during which participants kept their eyes closed. *B*, electrode layout. A custom 35 electrodes layout positioned along the 10–20 system (33 electrodes with a higher density in the parietal and occipital lines, plus two electrodes on the mastoids). *C*, grand average waveform for the P1 ROI of all participants (grey is pre-HFS, blue is post-HFS). Shaded areas indicate the SD at each time point. Stars depict the significance level of the paired *t* test on the amplitudes pre/post-HFS reported in (*E*): $t_{26} = -4.03$, $P < 0.001$, Cohen's $d = -0.371$. *D*, grand average waveform for the N1b ROI of all participants (grey is pre-HFS, blue is post-HFS). Shaded areas indicate the SD at each time point, and the yellow rectangle indicates the N1b component, computed as the mean value from the peak of N1 to the halfway point between N1 and P2. Stars depict the significance level of the paired *t* test on the amplitudes pre/post-HFS reported in (*F*): $t_{26} = 4.43$, $P < 0.001$, Cohen's $d = 0.504$. *E*, peak amplitude of the P1 waveform for each participant pre- and post-HFS. *P* value reported corresponds to paired *t* test post-HFS *vs.* pre-HFS: $t_{26} = -4.03$, $P < 0.001$, Cohen's $d = -0.371$. *F*, amplitude of the N1b waveform for each participant pre- and post-HFS. *P* value reported corresponds to paired *t* test post-HFS *vs.* pre-HFS: $t_{26} = 4.43$, $P < 0.001$, Cohen's $d = 0.504$. *G*, distribution of the P1 amplitude difference between post- and pre-HFS for the main and control experiments. *P* value reported corresponds to the ANOVA interaction between the factors TIME (pre/post-HFS) and HFS: $F_{1,10} = 5.251$, $P = 0.0449$. *H*, distribution of the N1b amplitude difference between post- and pre-HFS for the main and control experiments. *P* value reported corresponds to the ANOVA interaction between the factors TIME (pre/post-HFS) and HFS: $F_{1,10} = 0.511$, $P = 0.491$. [Colour figure can be viewed at wileyonlinelibrary.com]

The stimuli were presented on a Display++ monitor (120 Hz, 1920 × 1080 pixels, 32 inches, factory calibrated and gamma corrected; Cambridge Research System, Rochester, UK) placed outside the room and viewed through a window to reduce electronic noise from the display. The screen was linked to a computer (Dell Optiplex 7070; Dell Technologies Inc., Round Rock, TX, USA) with an NVIDIA GeForce 1050 graphics card (Nvidia Corporation) running Windows 11 and the stimuli were designed and presented using MATLAB, R2023a (The MathWorks Inc.) and Psychtoolbox-3 (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997). Through the Display++ Psychtoolbox interface, TTL triggers were generated and sent to the Biosemi ActiveTwo recording box on the first frame of stimulus presentation. These triggers were recorded alongside the EEG data in the Biosemi Dataformat (BDF) file and used offline to epoch the data (see section on EEG pre-processing).

The stimuli consisted of circular black and white checkerboards (size: 4°, check size: 0.25°, spatial frequency: 2 cpd, contrast: 64%) centred at 4° above the central fixation cross (size: 0.5°) on a grey background (luminance: 110 cd m^{-2}, CIE: $x = 0.305$, $y = 0.332$). The contrast of the stimulus was inverted after every presentation, such that successive stimuli had opposite contrasts to avoid adaptation. The checkerboard was presented for 33 ms, followed by a grey screen until the next stimulus was presented.
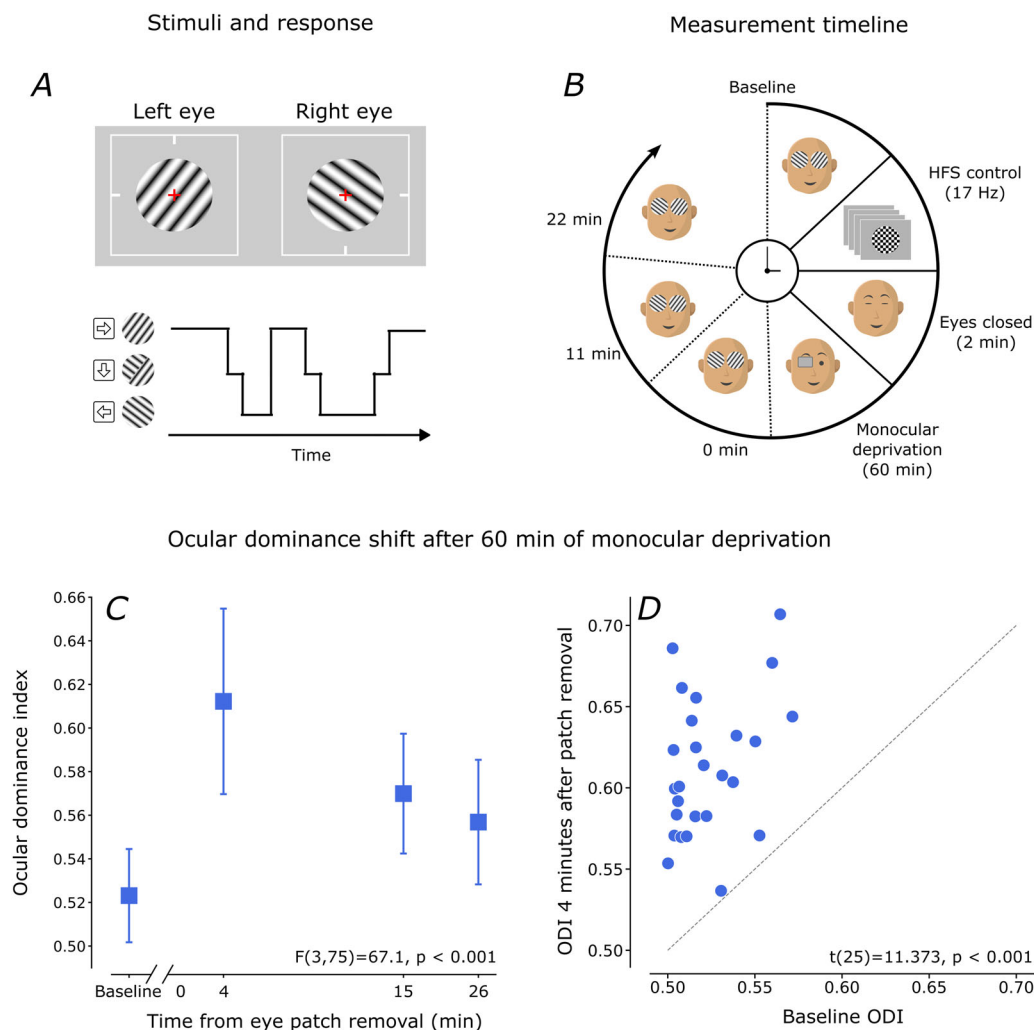

Figure 2. Experimental design and results: homeostatic plasticity paradigm
A, diagram of the stimuli and response paradigm for binocular rivalry measurement of OD. *B*, experimental paradigm timeline. Baseline OD was measured before a 2 min 17 Hz high-frequency visual stimulation (HFS). After this HFS block, participants closed their eyes for 120 s, and then were monocularly deprived for 60 min. Ocular dominance was measured again immediately after the end of deprivation, then 11 min after the end, and a final measurement was made 22 min after the end of deprivation to monitor the recovery of the OD. *C*, mean OD index (ODI) for every measurement. Error bars represent the SD. *D*, scatter plot of the baseline ODI against the ODI measured immediately after the end of deprivation for individual participants. [Colour figure can be viewed at wileyonlinelibrary.com]

The position of the checkerboard (centred 4° above the central fixation cross) was chosen after a pilot experiment showed this position as the most reliable to induce the VEP we were aiming to record. The size and contrast of the checkerboard were chosen to match the size and contrast of the stimuli used in the binocular rivalry paradigm.

Procedures

Each participant took part in four independent experimental conditions, in a counterbalanced order, with each experimental session separated by at least 24 h.

Two conditions measured the effect of Hebbian and homeostatic plasticity independently, whereas the other two conditions assessed the interaction between these two forms of plasticity, inducing both types of plasticity simultaneously.

Independent conditions:

- Homeostatic plasticity: effect of short-term (1 h) MD on OD measured by means of binocular rivalry (Fig. 2*B*).
- Hebbian plasticity: effect of 8.6 Hz HFS (Fig. 1*A*), on VEPs amplitude.

The interaction conditions were:

- Homeostatic on Hebbian plasticity: effect of short-term MD on the modulation of VEPs amplitude induced by HFS (Fig. 4*A*).
- Hebbian on homeostatic plasticity: effect of HFS on the OD shift induced by short-term MD (Fig. 4*B*).

A control condition was also performed on a subset of the participants ($N = 11$) to ensure the effect of the HFS paradigm, in which the HFS block was withheld between the first and second measurement of Hebbian plasticity to assess the effect of adaptation in the VEPs amplitude modulation.

Homeostatic plasticity. To measure homeostatic plasticity, we recorded OD at baseline, then presented the participants with a non-LTP inducing HFS block (see final paragraph in this section) before we monocularly deprived their dominant eye (as measured during the inclusion binocular rivalry test) for 60 min. After the end of the deprivation, we measured OD three more times: immediately after removing the eye patch, 11 min after the removal of the eye patch and 22 min after, which provided participants with a 3 min break in between recording sessions after the end of deprivation (a timeline of the recording sessions is provided in Fig. 2*B*).

Each OD measurement session consisted of four blocks, each lasting 90 s. Before each block, observers were presented with only the surrounding square frame and the fixation cross until they achieved stable dichoptic fusion, characterized by perceiving a single frame with vertically and horizontally aligned vergence rectangles (Fig. 2*A*). One OD measurement session lasted 8 min and included three breaks: a 15 s break after the first block, a 30 s break after the second block and another 15 s break after the third block.

During the 90 s blocks, the orthogonal gratings were presented continuously, one in each eye. Participants had to continuously report their perception using the arrow keys on the keyboard (left arrow for counterclockwise tilted grating, right arrow for clockwise tilted grating, down arrow for mixed percept). The orientation of the gratings was swapped between the eyes at each block, so that each eye saw each orientation twice for each measurement session.

For this session, the checkerboard used to induce HFS in the Hebbian plasticity paradigm (see section on Homeostatic plasticity) was flashed 2000 times at a rate of 17 Hz (no stimulus onset asynchrony (SOA), because the frame rate of the screen did not allow a sufficiently narrow range of frequencies to guarantee a stable average frequency), which lasted the same duration as the 8.6 Hz HFS block, but has been reported to not induce LTP-like effects (Hamm et al., 2005; Kirk et al., 2010).

Hebbian plasticity. To measure Hebbian plasticity in the participants, we adapted a previously reported paradigm (Ross et al., 2008; Teyler et al., 2005): we measured VEPs in response to transient visual stimuli (checkerboards) before and after a 2 min HFS using the same visual stimulus.

Each VEP measurement (pre- and post-HFS) consisted of two blocks of 250 stimuli presentations [stimulation frequency: 0.8 Hz, stimulus duration: 33 ms, interstimulus interval (ISI): 600–1500 ms, 500 presentations in total, the contrast of the checkerboard was inverted after every presentation to reduce adaptation], with a short 15 s break after 125 presentations. Each block lasted around 5 min and was followed by a 30 s break before the next block started, upon a key press on the keyboard. A full measurement lasted on average 12 min, including breaks.

The number of stimulus presentations (500 per measurement) was decided based on previous studies. The original study by Teyler et al. (2005) used 420 presentations, 210 per hemifield, and Lunghi, Berchicci, et al. (2015) delivered 800 presentations to each eye to measure the VEP components they were investigating. The number of stimulus presentations in the present study was chosen to achieve the best signal to noise ratio for every participant with a reasonable time spent in the room (as tested in pilot experiments), given the time constraints of our interaction condition involving MD, as the effect of MD decays within 15–20 min from eye-patch removal (see Discussion).

After the pre-HFS measurement, participants underwent an HFS block designed to modulate the amplitude of the VEP we recorded in this paradigm. This HFS block followed the paradigm of the original studies (Ross et al., 2008; Teyler et al., 2005) and consisted of 1000 checkerboard presentations at a rate of 8.6 Hz (SOA: 67–100 ms, the contrast of the stimulus was inverted after every presentation to avoid adaptation) which lasted around 2 min. This was followed by 120 s of break with eyes closed, after which the next VEP measurement (post-HFS) started upon a key press on the keyboard.

To ensure that participants kept a stable fixation during the VEP recording and that they kept their attention focused on the visual stimuli (Lunghi, Berchicci, et al., 2015), during each measurement block, an attentional control was performed by changing the colour of the fixation cross regularly (every 6 s on average, interval range: 4–8 s) and asking observers to report the number of times the fixation cross had changed colour during the block. This number was reported at the end of the block, before the 30 s break, and participants were excluded if their response differed from the actual number by more than 10.

Homeostatic on Hebbian plasticity interaction. To investigate how homeostatic plasticity would impact Hebbian plasticity, 60 min MD was performed just before the VEP+HFS paradigm, following the exact same procedure described in the section on Homeostatic plasticity. A detailed timeline is provided in Fig. 4*A*.

Hebbian on Homeostatic plasticity interaction. To investigate how Hebbian plasticity could impact homeostatic plasticity, we replaced the non-LTP inducing HFS block with the HFS block used to induce Hebbian plasticity (1000 presentations of the checkerboard pattern at a frequency of 8.6 Hz followed by a 120 s break with eyes closed. A detailed timeline is provided in Fig. 4*D*.

Control condition. An additional control condition was included for a subgroup of participants ($N =$ 11), consisting of replication of the Hebbian plasticity paradigm, but without HFS: during the 2 min following the 'pre-HFS' measurement, participants kept their eyes open and fixated on the cross, but no flashing of the checkerboard pattern was presented. This condition was added to ensure that the 8.6 Hz HFS block induced the effect measured using the VEP paradigm (see section on Hebbian plasticity: high-frequency stimulation modulates the P1 component but not the N1b component of the visual evoked potential).

Data and statistical analyses

EEG pre-processing. The EEG data (saved in BDF format) were analysed offline using Python, version 3.12 (Python Software Foundation, Wilmington, DE, USA and MNE-Python (Gramfort, 2013; Larson et al., 2024).

First, the raw data from the custom 35 channel setup were visually inspected for bad channels (flat or saturated), which were then reconstructed using spherical splines interpolation via the interpolate_bads function in MNE-Python. After reconstructing the bad channels, a copy of the raw data were prepared for an automated Independent Component Analysis (ICA) artifact rejection tool, ICLabel (Pion-Tonachini et al., 2019), implemented in the mne-icalabel package. This preparation involved filtering the raw data between 1 and 100 Hz and re-referencing it to the average reference. The ICLabel algorithm performs ICA on the signal and categorizes each component into one of seven categories. We retained the components labelled as 'brain' and 'other', removing the remaining components from the original (unfiltered and not referenced) signal.

After applying the ICA correction, the signal was band-pass filtered between 0.1 and 30 Hz and re-referenced to the average of the channels. Using the triggers recorded during the stimulus presentations, we segmented the raw signal into 600 ms epochs, with 100 ms pre-stimulus and 500 ms post-stimulus, rejecting epochs with signal exceeding 70 μV.

To create the final VEPs, we averaged the epochs based on their blocks (pre- or post-HFS), resulting in one VEP trace before and after HFS for each electrode, each session and each participant.

VEP analysis. We investigated the VEPs reported to be impacted by the paradigm described by Teyler et al. (2005) and other studies, focusing on the P1 and N1b components.

As a result of high inter-individual variability in the scalp topography of these evoked potentials (Allison et al., 1977; Di Russo et al., 2002; Di Russo, 2003; Di Russo & Pitzalis, 2014), we defined an observer-specific region-of-interest (ROI), consisting of four electrodes that showed the highest amplitude for these evoked potentials during the baseline VEP measurement of each session (first 500 stimulus presentations, before HFS). We then averaged the waveforms from these electrodes to create a single VEP trace for P1 and another VEP trace for N1b.

We defined P1 as the highest positive peak in the VEP traces that does not reverse polarity between the hemispheres and has a peak latency between 85 and 150 ms, as reported to be elicited by upper visual field stimulation by Di Russo et al. (2002). We defined N1 as the first negative peak after P1, and P2 as the next major positive peak after N1. Identical to the paradigm of Teyler et al. (2005),

we defined N1b as the mean amplitude between N1 and hallway through P2.

To identify the best electrodes for each observer ROI, we investigated the 'pre-HFS' VEP traces to find the best peak amplitudes independently of the effect we were investigating. The same group of electrodes was used to measure the 'post-HFS' amplitudes, but different ROIs were selected for different conditions because of differences in electrode placements across different days (for individual clusters for each participant and session, see the Supporting information, Table S1 and S2).

Once we selected the ROI, we averaged the electrode subset signal separately for the pre- and post-HFS conditions and compared the amplitude of the VEP of interest for that subset using SciPy's find_peaks function.

OD measurement. To measure OD, we compute the OD index (ODI) following Lunghi et al. (2013): $\text{ODI} = \frac{T_{deprived}}{T_{deprived} + T_{non\ deprived}}$, where T is the total time where the observers reported complete dominance of the visual stimulus presented to either the deprived or not-deprived eye.

Hebbian plasticity: effect of HFS on the amplitude of VEPs. To quantify the effect of HFS on the amplitude of VEPs components, we used a paired-samples t test to compare the amplitude of the P1 and N1b components, respectively, before and after the HFS block (Fig. 1*E* and *F*).

Homeostatic plasticity: effect of short-term MD on OD. To quantify the effect of 60 min of MD on OD, we used a 1×4 repeated-measures ANOVA: $F_1 = \text{TIME}$ from the end of deprivation (Baseline, 4, 15 and 26 min) to assess the effect of MD on the OD measurements acquired before and after MD.

Homeostatic on Hebbian plasticity interaction. To quantify the interaction of homeostatic plasticity on Hebbian plasticity, we compared the change in amplitude of the VEP components before and after the HFS block with and without 60 min of MD. To do so, we used a 2×2 repeated-measures ANOVA: $F_1 = \text{TIME}$ (pre/post-HFS), $F_2 = \text{MD status}$ (MD, noMD) (Fig. 4*B* and *C*).

In Fig. 4*B* and *C*, we show the amplitude difference in the P1 VEP component from pre-HFS to post-HFS by subtracting the amplitude of the pre-HFS VEP from the amplitude of the post-HFS VEP, such that a negative value in these graphs represents a decrease in the amplitude of the component.

Hebbian on homeostatic plasticity interaction. To quantify the interaction of Hebbian plasticity on homeostatic plasticity, we compared the change in OD from baseline (by subtracting the baseline value from the three

measurements after the end of deprivation, such that a positive value indicates a strengthening of the eye that was deprived) with and without Hebbian plasticity inducing HFS. To do so, we used a 3×2 repeated-measures ANOVA: $F_1 = \text{TIME}$ from the end of deprivation (4, 15 and 26 min), $F_2 = \text{HFS status}$ (HFS, noHFS).

In Fig. 4*E* and *F*, we show the change in OD from baseline after the end of deprivation by subtracting the baseline value of the ODI from the ODI measured at each time point, such that a positive value indicates an increase in the dominance of the eye that was deprived.

Correlations between HFS and MD. To investigate a possible correlation between Hebbian and homeostatic plasticity across participants, we used Spearman correlation on the difference in amplitude of the P1 VEP before and after HFS (without MD) and the change in ODI from baseline immediately after the end of deprivation (without HFS).

The amplitude difference before and after HFS for P1 is computed by subtracting the pre-HFS value from the post-HFS value of the P1 component, such that a negative value shows a decrease in the amplitude of the P1 VEP component.

The change in ODI from baseline is computed by subtracting the baseline value from the ODI value measured immediately after the end of deprivation, such that a positive value indicates a strengthening of the eye that was deprived.

Statistical power. To quantify the risk of a type II error (false rejection of the null hypothesis), we computed the minimum detectable effect sizes (Bloom, 1995) for the null results concerning the interaction between Hebbian and homeostatic plasticity. We used G*Power software (Faul et al., 2007) with $\alpha = 0.05$ and $\beta = 0.2$ ($1 - \beta = 0.8$), common values used in the literature (Cohen, 2013) and used the correlation coefficients reported in this manuscript when prompted by the software. The minimum detectable effect sizes (i.e. MDES) for the interaction were calculated to be Cohen's $f = 0.26$ for the binocular rivalry paradigm and $f = 0.31$ for the VEP paradigm, both of which correspond to medium-sized effects according to Cohen's conventions. For the interpretation of these results, see Discussion.

Results

We investigated the interplay between homeostatic and Hebbian visual plasticity in adult humans. To this aim, we used two established experimental paradigms: short-term MD to induce visual homeostatic plasticity (Castaldi et al., 2020; Lunghi et al., 2011, 2013; Zhou et al., 2013) and the modulation of VEPs induced by HFS to induce Hebbian

plasticity (Kirk et al., 2010; Sumner et al., 2020; Teyler et al., 2005). We probed each type of plasticity in isolation (homeostatic plasticity, Fig. 2; Hebbian plasticity, Fig. 1) and in combination with the other one (Fig. 4).

Homeostatic plasticity: Short-term MD shifts OD in favour of the deprived eye

We probed short-term visual homeostatic plasticity, by assessing the effect of short-term MD on OD measured by means of binocular rivalry (Fig. 2*A*). We computed an OD index (ODI, see section on Binocular rivalry) based on the dominance duration of each eye as reported by the observers, before and for 30 min after a short period (60 min) of MD, preceded by 2 min of 17 Hz HFS (Fig. 2*B*). Consistently with previous studies (Baroncelli & Lunghi, 2021; Lunghi et al., 2011, 2013), we found that short-term MD induced a change in OD in favour of the deprived eye (Fig. 2*C*), which lasted for up to 30 min after eye-patch removal. A 1 × 4 repeated-measures ANOVA (TIME from the end of deprivation) revealed a significant main effect of factor TIME: $F_{3,75} = 67.12$, $P < 0.001$, $\eta^2 = 0.729$.

Hebbian plasticity: HFS modulates the P1 component but not the N1b component of the VEP

We probed short-term Hebbian plasticity by testing the effect of HFS on the amplitude of VEPs in adult humans, following the paradigms of Teyler et al. (2005) and Ross et al. (2008). VEPs were recorded in response to transient visual stimuli (checkerboards, Fig. 2*A*), using a customized 35 electrode layout (Fig. 1*B*). HFS involved 1000 flashes at an average temporal frequency of 8.6 Hz of the stimulus used to measure the VEPs (Fig. 1*A*). Our results showed a reduction in the amplitude of the P1 VEP component (paired *t* test: $t_{26} = -4.03$, $P < 0.001$, Cohen's $d = -0.371$) and the N1b component (*t* test: $t_{26} = 4.43$, $P < 0.001$, Cohen's $d = 0.504$) after the HFS block (Fig. 1*C* and *D*).

Because this effect contradicts the findings of Teyler et al. (2005) and Ross et al. (2008) and may suggest visual response adaptation rather than the expected LTP-like changes (but see also Discussion for other studies showing a decrease in amplitude after this HFS paradigm), we conducted a control experiment on a subset of participants (N = 11) to verify the impact of the HFS block on the change in amplitude of the VEP components. We replaced the HFS block in the VEP paradigm with 120 s of sustained attention on a fixation cross surrounded by a grey background, followed by 120 s with eyes closed. We measured the amplitudes of the P1 and N1b components for the first 500 epochs and the last 500 epochs and compared them as 'pre' and 'post' HFS. The results from this control experiment (Fig. 1*G* and *H*) were analysed using a 2 × 2 repeated-measures ANOVA

[TIME (pre/post-HFS) × HFS STATUS (HFS/no HFS)] separately for P1 and N1b. For P1, the analysis revealed a significant main effect of TIME ($F_{1,10} = 7.09$, $P = 0.0237$) and a significant interaction between TIME and HFS STATUS ($F_{1,10} = 5.251$, $P = 0.0449$), confirming that the HFS block influenced the VEP amplitude change for P1, and no significant effect of HFS STATUS was found on its own ($F_{1,10} = 2.529$, $P = 0.143$). For N1b, the analysis showed a main effect of TIME ($F_{1,10} = 6.72$, $P = 0.0268$) but no significant effect of HFS STATUS ($F_{1,10} = 0.483$, $P = 0.502$) and no interaction between HFS STATUS and TIME ($F_{1,10} = 0.511$, $P = 0.491$). This indicates that the contribution of the HFS block to the reduction in amplitude of N1b measured in the main experiment was not significant, suggesting that the effect observed on the N1b component was primarily driven by adaptation to the stimulus. Therefore, we decided not to include the N1b amplitude change in further analyses and instead focused on the change in the P1 component as measure of short-term Hebbian plasticity, following other studies using the same component (Abuleil et al., 2019; Elvsåshagen et al., 2012; Klöppel et al., 2015; Normann et al., 2007; Zak et al., 2018).

Homeostatic and Hebbian plasticity correlate in adult humans

Having shown that both homeostatic and Hebbian plasticity can be reliably assessed in adult humans, we investigated whether these two forms of plasticity are related to each other (Fig. 3). To this aim, we explored a potential correlation between short-term visual

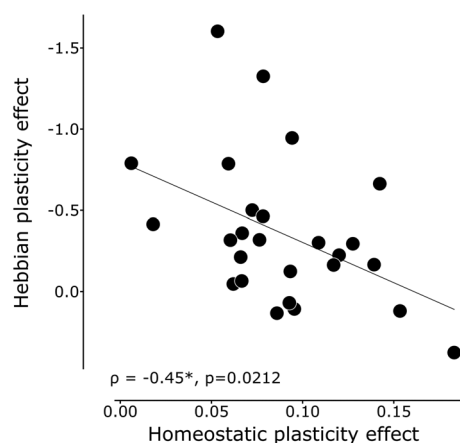Correlation between homeostatic and Hebbian plasticity

$\rho = -0.45^*$, p=0.0212

Figure 3. Correlation between the homeostatic and Hebbian plasticity effects across participants
Scatter plot of the homeostatic plasticity effect (ODI change from baseline observed after 60 min of MD) *vs.* the Hebbian plasticity effect (difference in P1 peak amplitude observed after HFS). Spearman's rho = −0.45, $P = 0.0212$.

homeostatic and Hebbian plasticity across participants. We defined homeostatic plasticity as the change in the ODI observed after 60 min of MD, and Hebbian plasticity as the change in amplitude of the P1 VEP component after HFS. We found a significant negative correlation between Hebbian and homeostatic plasticity across participants (Spearman's rho $= -0.45$, $P = 0.0212$), suggesting that participants who responded more strongly to one manipulation tended to respond more weakly to the other. This result could suggest related (potentially complementary) mechanisms for regulating short-term Hebbian and homeostatic plasticity in the adult brain.

Short-term homeostatic and Hebbian plasticity do not interact when induced simultaneously in adult humans

To investigate directly a potential interaction between homeostatic and Hebbian short-term visual plasticity, we performed two experimental conditions during which both types of plasticity were elicited at the same time and compared the plasticity effects to those measured when each form of plasticity was evoked in isolation.

To evaluate the influence of homeostatic on Hebbian plasticity, participants underwent 60 min of MD prior to measuring the effect of HFS on the P1 VEP amplitude, as shown in Fig. 4*A*. A 2 × 2 repeated-measures ANOVA [MD STATUS (MD/no MD) × TIME (pre/post-HFS)] showed a main effect of TIME ($F_{1,25} = 19.79$, $P < 0.001$, $\eta^2 = 0.21$), but no effect of MD STATUS ($P = 0.956$) and no interaction between TIME and MD STATUS ($P = 0.859$).

We also found a correlation across participants between the change in amplitude of the P1 VEP component for the independent and interaction protocols (Spearman's rho $= 0.417$, $P = 0.0338$) (Fig. 4*E*), indicating that the concurrent induction of homeostatic plasticity did not alter the Hebbian plasticity response, and good test-retest reliability of the effect. The results indicate that the 60 min MD protocol did not modulate the effect of HFS on the P1 amplitude, a measure of Hebbian plasticity in this paradigm. We also measured a reliable correlation between the pre-HFS P1 amplitude with and without 60 min MD (Spearman's rho $= 0.788$, $P < 0.001$) which shows a good test-retest reliability for the VEP measurement paradigm (see Supporting information, Fig. S1) and low intrasubject variability in the baseline amplitude of the P1 component.

To assess the influence of Hebbian plasticity on homeostatic plasticity, we presented participants with a Hebbian plasticity-inducing HFS stimulus immediately before the beginning of MD (Fig. 4*B*). A 2 × 3 repeated-measures ANOVA [HFS STATUS (HFS/no HFS) × TIME (from end of deprivation)] revealed a main effect of TIME

($F_{2,50} = 70.89$, $P < 0.001$, $\eta^2 = 0.459$), but no effect of HFS STATUS ($P = 0.409$) and no interaction between HFS STATUS and TIME ($P = 0.606$).

We also found a correlation across participants between the change in ODI from baseline after MD for the independent and interaction protocols (Spearman's rho $= 0.571$, $P = 0.00234$) (Fig. 4*F*), indicating that the concurrent induction of Hebbian plasticity did not alter the homeostatic plasticity response, and good test-retest reliability. This indicates that HFS had no impact on the change of ODI after 60 min of MD (Fig. 4*D* and *F*), a measure of homeostatic plasticity in this paradigm. Independently, we reproduced the test-retest reliability of the baseline ODI measurements across participants by measuring the correlation between the baseline measurements of the two binocular rivalry sessions, showing a very reliable OD at baseline, before 60 min MD (Spearman's rho $= 0.897$, $P < 0.001$) (see Supporting information, Fig. S2).

Discussion

We investigated the relationship between short-term Hebbian and homeostatic visual plasticity in adult humans by using two established paradigms to elicit each form of plasticity. We reliably induced homeostatic plasticity, as measured by the change in OD after short-term MD, and Hebbian plasticity, as measured by the modulation of the VEP P1 component amplitude following HFS. We found that, although Hebbian and homeostatic plasticity did not interact directly with each other when elicited at the same time, they were correlated across participants, indicating for the first time a relationship between these two forms of plasticity.

Our findings regarding short-term visual homeostatic plasticity are consistent with previous work (Chadnova et al., 2017; Lunghi et al., 2011, 2013; Wang et al., 2020; Zhou et al., 2013, 2015) showing that, even though the effect of MD builds up over time (Min et al., 2022; Prosper et al., 2023), 60 min of MD is sufficient to induce a reliable and measurable change in OD in adult humans. This effect has been reported to be mediated by reciprocal changes in interocular inhibition and excitation (Chadnova et al., 2017; Lunghi, Emir, et al., 2015) and shows evidence of preserved homeostatic regulation mechanisms in the visual cortex in adulthood (Binda et al., 2018; Lunghi, Emir, et al., 2015).

Regarding short-term Hebbian plasticity, the present study joins growing experimental evidence questioning the nature of the LTP-like effect observed in the human visual cortex with HFS. Indeed, several studies report that this HFS paradigm shows extreme individual variability and does not always induce the expected potentiation of VEP responses (Abuleil et al., 2019; Klöppel et al., 2015;

Lahr et al., 2014; Lengali et al., 2021; Porto et al., 2015; Sumner et al., 2020). Indeed, we failed to reproduce the modulation effect of the N1b component commonly reported by other studies (Kirk et al., 2010; McNair et al., 2006; Teyler et al., 2005) because the control experiment revealed that the change in N1b amplitude observed after HFS was primarily driven by adaptation to the stimulus rather than the HFS block. This difference may be a result of the change in position of the stimulus, being presented para-foveally in our paradigm compared to centrally in previous studies. Studies investigating the effect of stimulus eccentricity on the VEP response show that higher eccentricity usually lead to lower responses

(Yu & Brown, 1997). Another potential explanation for this difference could be linked to the number of stimulus presentations used to record VEPs. Indeed, other studies adapting the original paradigm (Kirk et al., 2010; Ross et al., 2008; Teyler et al., 2005) use shorter measurement blocks compared to ours (between 120 and 250, compared to 500 for our paradigm). Even though studies have shown that more presentations lead to better signal-to-noise ratio in VEP measurements (Boudewyn et al., 2018), we might be reaching a threshold between adaptation to the stimulus and signal-to-noise ratio improvements in this specific paradigm. Moreover, Ross et al. (2008) showed that the potentiation effect of their HFS paradigm

Homeostatic plasticity on Hebbian plasticity interaction
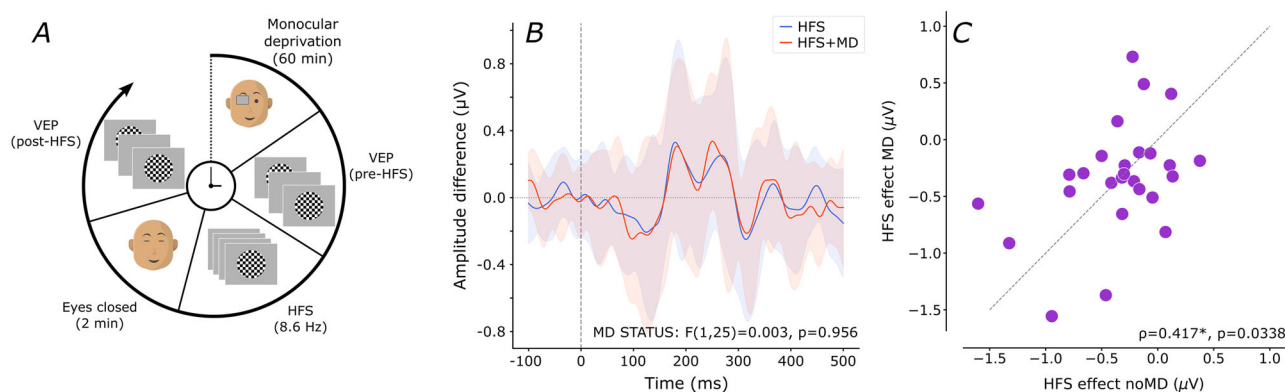
Hebbian plasticity on homeostatic plasticity interaction
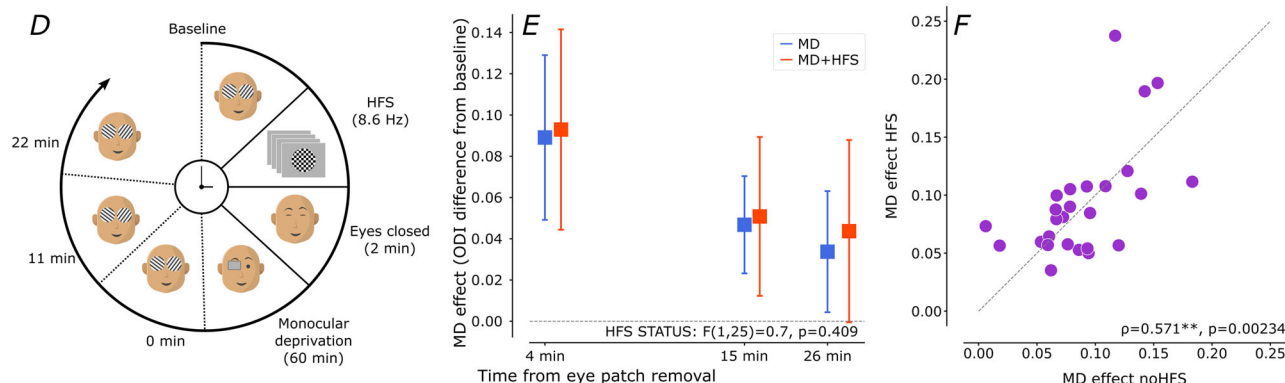

Figure 4. Experimental design and results: interaction paradigms *f*
A, timeline of the interaction experiment for the effect of homeostatic plasticity on Hebbian plasticity. Participants were deprived for 60 min prior to the start of the EEG recording. *B*, difference waves (post-HFS) – (pre-HFS) for independent and interacting measurements. Statistics show the result of the MD_STATUS factor in the 2 × 2 repeated-measures ANOVA test. Shaded areas indicate the SD for each time point. *C*, correlation between the Hebbian plasticity effect (P1 amplitude change (post-HFS) – (pre-HFS) for the independent (*x*-axis) *vs.* interaction (*y*-axis) conditions. Spearman's rho = 0.417, *P* = 0.0338. The dotted line is the identity line. *D*, timeline of the interaction experiment for the effect of Hebbian plasticity on homeostatic plasticity. Participants were exposed to 8.6 Hz high-frequency stimulation before the beginning of monocular deprivation. *E*, difference between baseline and post-deprivation OD index. Error bars represent SD. The dotted line represents baseline values. *F*, correlation between the homeostatic plasticity effect (change in OD from baseline for the first time point after MD) for the independent (*x*-axis) and interaction (*y*-axis) conditions. Spearman's rho = 0.571, *P* = 0.00234. Dotted line is the identity line. [Colour figure can be viewed at wileyonlinelibrary.com]

disappeared within the first measurement block post-HFS, and suggested a potential role of the VEP measurement (0.8 Hz, similar to the one we used in the present experiment) inducing an active depotentiation of the HFS effect. Although speculative, this role of the measurement frequency could explain the lack of effect on the N1b component because the effect could disappear much faster in our paradigm and only the adaptation to the stimulus would remain measurable.

Despite the non-replication of the N1b component modulation, we obtained a valid and reproducible measure of short-term Hebbian-like plasticity, because we found that high-frequency visual stimulation could reliably modulate the amplitude of the P1 component of the VEP. Although the effect (decrease in P1 amplitude after HFS) differs in its direction from the early studies conducted using the protocol introduced by Teyler et al.'s (Teyler et al., 2005), other studies found similar decreases in amplitude of the VEP components in EEG (Abuleil et al., 2019) and in fMRI activations (Lahr et al., 2014), suggesting that this protocol can induce both LTP-like and LTD-like effects on the VEP components. The average magnitude of the change in P1 component amplitude for our experiment is similar to that of Ross et al. (2008), on the order of 0.3 μV, suggesting that we did induce a similar Hebbian-like effect, if only in the opposite direction from their studies. Moreover, the control experiment performed on a subset of participants showed that the HFS block was crucial to induce the difference between pre- and post-VEP components, rather than just passive adaptation to the visual stimulus.

What about the interplay between short-term homeostatic and Hebbian plasticity?

Interestingly, we found that these two forms of plasticity were negatively correlated across participants, suggesting that participants who displayed stronger Hebbian plasticity tended to show weaker homeostatic plasticity, and vice versa. This negative correlation suggests that the two forms of plasticity may serve complementary roles in maintaining the stability of neuronal responses in the adult visual cortex. Specifically, Hebbian plasticity allows for the selective potentiation of responses to relevant sensory inputs (McNair et al., 2006; Ross et al., 2008), whereas homeostatic plasticity adjusts the overall balance of excitation and inhibition to stabilize average neural activity (Binda et al., 2018; Lunghi, Emir, et al., 2015). To our knowledge, this is the first demonstration of a direct relationship between homeostatic and Hebbian plasticity in adult humans.

A possible alternative explanation for this correlation is that the two effects probed here are both mediated by contrast adaptation: adaptation to high-contrast for the VEP modulation and adaptation to low-contrast for short-term MD. Although this is an intriguing explanation for the negative correlation observed, we

consider this to be improbable for several reasons. Regarding the Hebbian-like plasticity of VEPs, our protocol was designed to minimize contrast adaptation as much as possible: after the HFS, participants underwent a period of rest (eyes closed) of the same duration as the HFS block (2 min) and, during HFS, stimulus contrast was reversed at each presentation. Because the effect of adaptation lasts for the same duration as the adaptor presentation (Greenlee et al., 1991), a possible adaptation effect linked to the HFS block should decay within the rest period. Moreover, although contrast adaptation has a consistent effect on retinal activity, for visual cortical activity (measured with VEPs), adaptation does not occur between visual stimuli of different temporal frequencies: when the adaptor and the test stimulus differ in temporal frequency either no effect or an enhancement of the response is observed after adaptation (Heinrich & Bach, 2002). It is therefore improbable that our 8.6 Hz HFS would have induced adaptation in our measurement protocol, where we presented checkerboards at a much lower rate (0.8 Hz). However, because repeated stimulation at the same ISI induces a robust adaptation (Andrade et al., 2015), we performed an additional experiment to control for a possible adaptation between the baseline and the post-HFS block, for which the ISI was the same. As discussed above, we showed that the effect of HFS on the N1b component was entirely the result of our repeated testing (up to the power of our study, see discussion about statistical power), but the amplitude of the P1 component could not be accounted for by this effect alone (Fig. 1*G* and *H*). Finally, a previous study investigating a possible interaction between Hebbian-like plasticity induced by HFS and OD assessed by binocular rivalry already controlled for the possible effect of contrast adaptation (Abuleil et al., 2021). The main result of the study is that monocular HFS stimulation induces a shift in OD towards the non-stimulated eye (consistently with the depotentiation effect of HFS that we found), whereas monocular presentation of a static stimulus yielded to no change in OD, ruling out adaptation as the underlying mechanism for the effect of HFS (Abuleil et al., 2021). This result is in line with other reports of VEP depotentiation induced by similar HFS paradigms (Abuleil et al., 2019; Dias et al., 2022; Lahr et al., 2014; Sanders et al., 2018) and interpreted as a form of LTD-like Hebbian plasticity.

On the other hand a number of studies investigated a possible relationship between short-term OD plasticity and contrast adaptation, concluding that they are probably different processes; for a review, see Hess & Hyun Min (2023) and Başgöze et al. (2018). For example, unlike contrast adaptation (Blakemore & Campbell, 1969; Bjørklund & Magnussen, 1981; Heinrich & Bach, 2002; Movshon & Blakemore, 1973; Movshon & Lennie, 1979), the effect of short-term MD shows no specificity to spatial frequency (Zhou et al., 2014) or orientation, no

interocular transfer, but rather reciprocal changes between the eyes (Chadnova et al., 2017; Zhou et al., 2013), no cortical storage (Menicucci et al., 2022) and no chromatic selectivity (Lunghi et al., 2013; Zhou, Reynaud, Hess, et al., 2017). Moreover, although phase disparity has been shown to be irrelevant for contrast adaptation of complex stimuli (Webster & Miyahara, 1997), phase scrambling successfully induces OD plasticity in humans (Bai et al., 2017). Importantly, studies using alternative deprivation methods showed that the effect of short-term MD could also be induced with no reduction in contrast or image quality; for example, by adding a delay to one eye (Steinwurzel et al., 2023), by using a kaleidoscopic stimulus in one eye (Ramamurthy & Blaser, 2018), by using an adapted form of continuous flash suppression (Kim et al., 2017) or by shifting attention away from one eye (Song et al., 2023). Altogether, the evidence described above indicates that the effect of short-term MD cannot be reduced to adaptation to low contrasts, but rather reflects a form of short-term plasticity.

Both homeostatic and Hebbian plasticity have been shown to co-exist in the early visual cortex: several studies have shown that homeostatic plasticity induced by short-term MD affects early visual areas (Binda et al., 2018; Lunghi, Emir, et al., 2015) and the Hebbian-like effect of HFS has been localized to areas V2 and V3, where the VEP components it affects are also located (Di Russo et al., 2002; Lahr et al., 2014). However, even if homeostatic and Hebbian plasticity act in the same areas, they are mediated by different neurotransmitters that induce different effects in those areas. This same spatial target but different induction processes may explain the correlation but lack of interaction between these two forms of plasticity. Specifically, animal studies have shown that pharmacological blocking of NMDA and AMPA receptor function inhibits the stimulus-response modulation effect (Cooke & Bear, 2014). The dependence of Hebbian plasticity upon NMDA and AMPA receptors, has also been confirmed in humans by Forsyth et al. (2015), who showed that augmenting NMDA receptor activity in humans improved the effect of HFS on VEP amplitudes. On the other hand, studies on both animal models (Harauzov et al., 2010; Hensch et al., 1998; Heimel et al., 2011) and humans (Lunghi, Emir, et al., 2015) have shown that homeostatic plasticity is mainly mediated by GABAergic inhibition in the primary visual cortex. This would suggest that these two forms of plasticity operate through different neurotransmitters (glutamate and GABA) underlying different functions (excitation and inhibition) and may have different regulation mechanisms. This could explain both their lack of inter-action when induced simultaneously and the negative correlation observed between homeostatic and Hebbian plasticity because, to maintain excitation/inhibition balance in the visual cortex, glutamate and GABA need to be modulated in the same direction (more

excitability would promote Hebbian plasticity, but would require more inhibition to avoid excitation/inhibition imbalance, and therefore a more limited homeostatic plasticity potential). Alternatively, we can speculate that the negative correlation that we found between homeostatic and Hebbian plasticity might reflect a more direct interplay between regulatory homeostatic mechanisms and Hebbian mechanisms. We can hypothesize that a system retaining a weaker potential for homeostatic plasticity and regulation would allow the tetanic stimulus to drive neuronal spiking to much higher levels, resulting in a stronger short-term LTP/LTD effect. On the other hand, a system with a strong potential for homeostatic regulation would limit the increase in spiking, leading to a weaker LTP/LTD response.

A possible explanation for the lack of interaction between the different forms of plasticity could be that the levels of Hebbian and homeostatic plasticity we elicited were insufficient to generate a detectable interaction. If these two forms of plasticity require common neural resources, the magnitudes of the effects that we observed may have been too low to induce a resource shortage that would lead to an interaction. In this case, because the effect of MD scales with the duration of deprivation (Min et al., 2022; Prosper et al., 2023), using a longer deprivation duration (e.g. 2 h) might have led to a stronger homeostatic response and a larger interaction. However, we consider that this probably would not change our results because the effect of MD is already strong and reliable after 1 h of deprivation and it is still present when we induced Hebbian plasticity (MD effect still significant 11 min after the end of deprivation). Using a different HFS paradigm to induce stronger effects could also be key to reaching an interaction threshold: the effect reported by other paradigms of HFS (notably [Normann et al., 2007]) involve longer stimulation and appear to induce a stronger effect ($\sim$1–2 μV in amplitude, or a 20% change in amplitude for each individual), but their stimulation paradigm is much longer (10 min of slow, 2 Hz oscillations) and would exceed the time course of the MD effect.

An alternative explanation for the lack of interaction between Hebbian and homeostatic plasticity in the present study could also be the differing temporal dynamics of these two forms of plasticity. Short-term Hebbian plasticity induced by HFS has been found to develop rapidly, within minutes (Teyler et al., 2005), but the onset and time course of this effect remains debated in the literature, with reports ranging from immediate to 10–30 min after induction (Lahr et al., 2014; Normann et al., 2007; Ross et al., 2008; Spriggs et al., 2018; Sumner et al., 2020). By contrast, the effect of MD on homeostatic plasticity is more well-established, with the effect accumulating gradually over the deprivation period and decaying exponentially after eye patch removal (Lunghi et al., 2013; Min et al., 2022;

Prosper et al., 2023). Given these disparate time courses, it is unclear whether the Hebbian effect elicited by HFS protocol could meaningfully interact with the homeostatic effect induced by MD within the context of the binocular rivalry experiment. However, this explanation is improbable given that the temporal dynamics of MD-induced homeostatic plasticity encompass the various timescales reported for HFS-induced Hebbian plasticity in prior research, and our study should have been capable of detecting an interaction in the binocular rivalry paradigm. Further studies might nevertheless benefit from testing the effect of HFS at a later time (longer than the 10 min in the present study) to shed light on potential late effects of the HFS procedure that could not be captured in our paradigm.

Another possibility could be the limited statistical power because of the sensitivity of our measurement. However, the minimum detectable effect sizes (i.e. MDES) for the interaction for both the binocular rivalry paradigm and the VEP paradigm corresponded to medium-sized effects. This indicates that our study was adequately powered to identify medium to large interactions, albeit smaller effect sizes may have remained undetected. Additionally, the high inter-individual variability associated with the two experimental manipulations might increase the error variance, making it more challenging to detect effects of small magnitude. It is therefore possible that subtle interactions between Hebbian and homeostatic plasticity exist but were not captured as a result of both the inherent sensitivity limitations of our experimental design and the elevated variability among participants.

One final factor of our experimental design that may have hindered the detection of an interaction effect is the stimulus specificity of the Hebbian plasticity changes induced by HFS protocol (McNair et al., 2006; Ross et al., 2008). Specifically, we achieved HFS using a checkerboard stimulus, following the original design by Teyler et al. (2005) and, although we matched the size and contrast of the HFS stimulus to the gratings used in the binocular rivalry experiment, the stimulus-specific nature of the Hebbian plasticity effects may have prevented any meaningful interaction between the HFS-induced Hebbian plasticity and the MD-induced homeostatic plasticity in the binocular rivalry paradigm. Moreover, because the HFS was applied binocularly, it probably did not elicit any significant monocular changes in OD that could be detected using the binocular rivalry paradigm. A study investigating the effect of monocular HFS on OD (Abuleil et al., 2021) showed that HFS delivered to one eye did induce a change in OD, in favour of the eye that was not stimulated. This suggests that inducing HFS monocularly could be a key to unlocking interaction mechanisms in future studies.

Some previous studies have utilized gratings to induce HFS, rather than checkerboards, demonstrating

orientation specificity of the HFS stimulation effect (McNair et al., 2006; Ross et al., 2008). Future research investigating the interaction between orientation-specific response potentiation and the effect of short-term MD on OD as assessed by binocular rivalry could address the interaction between eye and stimulus selectivity of both effects. Furthermore, presenting the VEP and HFS stimuli foveally rather than para-foveally could potentially provide more opportunity for the two phenomena to interact because short-term homeostatic plasticity is usually probed using a central visual task.

Our findings, along with the broader literature, suggest that future studies could benefit from meticulously calibrating stimuli to target specific VEP components and to maximize the interaction opportunities between HFS and short-term MD. An unresolved issue remains whether the optimal parameters for one technique are equally optimal for the other. Notably, prior HFS studies have employed larger stimuli with a higher spatial frequency, which are not well-suited for binocular rivalry setups because of the increased risk of overlap and contamination between stimuli presented to each eye, as well as lower levels of exclusive dominance with higher spatial frequency stimuli (O'Shea et al., 1997).

The heterogeneous findings of our experiment may reflect the intricate nature of experience-dependent plasticity in the human visual cortex, which probably involves a delicate balance between diverse plasticity mechanisms, each serving a distinct purpose in preserving the optimal function of the visual system.

In conclusion, our results suggest a largely preserved plastic potential in the visual cortex of the adult brain, for both short-term homeostatic and Hebbian plasticity. Importantly, we found that these two forms of plasticity are inversely correlated in their magnitude, suggesting, for the first time, a relationship between homeostatic and Hebbian plasticity in the adult human visual cortex. The negative correlation between Hebbian and homeostatic plasticity in individuals could have important clinical applications, allowing therapies to be tailored to the specific 'plasticity profile' of each individual: based on the ratio between Hebbian and homeostatic plasticity potential (which can be easily and non-invasively measured with the experimental paradigms presented here), some patients may respond better to different forms of treatment. A paradigmatic case is the treatment of amblyopia after the closure of the critical period. Several treatments for adult amblyopia have been proposed in recent years, with some relying on Hebbian plasticity [perceptual learning (Astle et al., 2011; Levi, 2005), dichoptic training (Hess et al., 2010; Li et al., 2013; Vedamurthy et al., 2015) and brain stimulation (Spiegel et al., 2013; Thompson et al., 2008)] and others relying on homeostatic plasticity reverse patching with (Lunghi, Sframeli, et al., 2019) or without (Zhou et al., 2019)

physical exercise. Targeting the 'right' modality to train in patients, depending on their plasticity profile, could lead to better outcomes in their recovery.

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Additional information

Data availability statement

Competing interests

The authors declare that they have no competing interests.

Authors contributions

A.P. and C.L. were responsible for conceptualization and methodology. A.P. was responsible for software. A.P. and T.B. were responsible for formal analysis, investigations and data curation. A.P., T.B. and C.L. were responsible for writing the original draft. A.P. was responsible for visualization. C.L. was responsible for validation, resources, reviewing and editing, supervision, project administration and funding acquisition.

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Supporting information

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