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The ups and downs of sensory eye balance: Monocular deprivation has a biphasic effect on interocular dominance

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ABSTRACT

Classic studies of ocular dominance plasticity in early development showed that monocular deprivation suppresses the neural representation and visual function of the deprived eye. However, recent studies have shown that a short period of monocular deprivation (<3 h) in normal adult humans, shifts sensory eye dominance *in favor* of the deprived eye. How can these opposing effects be reconciled? Here we argue that there are two systems acting in opposition at different time scales. A fast acting, stabilizing, homeostatic system that rapidly decreases gain in the non-deprived eye or increases gain in the deprived eye, and a relatively sluggish system that shifts balance toward the non-deprived eye, in an effort to reduce input of little utility to active vision. If true, then continuous deprivation should produce a biphasic effect on interocular balance, first shifting balance away from the non-deprived eye, then towards it. Here we investigated the time course of the deprivation effect by monocularly depriving typical adults for 10 h and conducting tests of sensory eye balance at six intervening time points. Consistent with previous short-term deprivation work, we found shifts in sensory eye dominance away from the non-deprived eye up until approximately 5 h. We then observed a turning point, with balance shifting back towards the non-deprived eye, -, a biphasic effect. We argue that this turning point marks where the rapid homeostatic response saturates and is overtaken by the slower system responsible for suppressing monocular input of limited utility.

1. Introduction

Within a critical period of development (Berardi et al., 2000), long-term monocular deprivation is marked by a permanent reduction in the deprived eye's visual function and neural representation in monocular and binocular visual areas (Hubel et al., 1977; Hubel & Wiesel, 1970; Wiesel, 1982). In humans as well, early monocular deficits (strabismus, refractive error, or cataracts) may lead to amblyopia and permanent loss of functional vision in the affected eye (Doshi & Rodriguez, 2007; Kiorpes & Daw, 2018; Maurer & McKee, 2018). Indeed, it is this plasticity in the developing visual system that underlies the *treatment* for amblyopia, which, alongside correction of the underlying monocular deficit, involves patching the stronger eye in an effort to increase representation of the amblyopic eye. Here, outcomes are better with longer duration (2–6 h per day, over weeks) of occlusion (Stewart et al., 2004), and, consistent with critical periods, when treated at younger ages (Epelbaum et al., 1993; Hensch & Quinlan, 2018; Scheiman et al., 2005).

However, there is growing evidence for a permanently plastic human brain (Pascual-Leone et al., 2005; Zilles, 1992) and specifically, visual cortex (Boroojerdi et al. (2001), for reviews, see Karmarkar & Dan (2006) and Karni & Bertini (1997)). Evidence for ocular dominance plasticity in adults is implied by the effectiveness of perceptual learning (Bavelier et al., 2010) to treat stereoblindness (Ding & Levi, 2011) and amblyopia (Huang et al., 2008; Levi, 2006; Li et al., 2011; Polat et al., 2004; Zhou et al., 2006). However, there is very little literature on the effect of long-term monocular deprivation, per se, on ocular dominance plasticity in adult humans. It has been shown that two days of monocular deprivation reduces excitability (as measured by detection of TMS-induced phosphenes) in both visual cortices (Lou et al., 2011), and that three days of monocular deprivation increases plasticity (as measured by susceptibility to perceptual learning) of the non-deprived eye (Shibata et al., 2012). Turning again to the amblyopia literature, there is evidence that if compliance with patching regimes (typically, several hours over several days) is high, it *can* be an effective treatment in adults (Holmes & Levi, 2018; Simonsz-Tóth et al., 2019; Wick et al., 1992). While paradigms and effect sizes vary, a consistent picture seems

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to emerge: throughout the lifespan, to deprive an eye is to shift balance toward the non-deprived eye (for a review, see Dahlhaus and Levelt (2010)).

This made it all the more surprising when recent work in adult humans showed that short-term (<3 h) of monocular deprivation actually shifts balance *away* from the non-deprived eye. This effect was first observed on the dynamics of binocular rivalry, where 2.5 h of deprivation shifted rivalry dominance in favor of the deprived eye (Lunghi et al., 2011). This effect has since been shown on dichoptic phase combination, global motion coherence, and contrast matching tasks (Zhou, Clavagnier, et al., 2013), and with various methods, including light-tight, diffuser, phase scrambling (Zhou et al., 2014), continuous flash suppression (Kim et al., 2017), and kaleidoscopic (Ramamurthy & Blaser, 2018) deprivation. (Short-term deprivation has even been suggested as a treatment for amblyopia with, counter-intuitively, a patching of the *stronger* eye (Zhou, Thompson, et al., 2013)). Most plausibly, the discrepancy that deprivation creates between the eyes' monocular images triggers both feedforward and feedback (Ramamurthy & Blaser, 2018) signals to interocular contrast gain control mechanisms (Moradi & Heeger, 2009; Shapley & Enroth-Cugell, 1984; Sperling and Ding, 2006). Gain is then increased in the deprived eye and/or decreased in the non-deprived eye in a rapid (Min et al., 2018), assumedly homeostatic, compensatory attempt to restore interocular balance (Lunghi et al., 2015; Ooi & He, 2020; Spiegel et al., 2017). Upon resumption of normal binocular vision, observed deprivation effects, then, reflect the persistence of this reweighting, giving the deprived eye greater inhibitory influence over the contralateral eye (Chadnova et al., 2017) and thereby greater representation in binocular/dichoptic tasks and percepts (Kim et al., 2017; Lunghi et al., 2011; Ramamurthy & Blaser, 2018; Zhou, Clavagnier, et al., 2013). This effect is relatively short-lived, persisting for 30 (Zhou, Clavagnier, et al., 2013), 60 min (Min et al., 2019), or 180 min (Lunghi et al., 2013). (Indeed, this "return to baseline" after resumption of binocular vision almost certainly reflects the action of this same homeostatic mechanism.)

Here we argue that these long-term and short-term effects in typically developed adult humans can be reconciled by supposing that there are two opposing processes at play. When a mismatch between the eyes is induced, a rapid, compensatory response is triggered that shifts balance away from the non-deprived eye, toward the deprived one, in an effort to restore interocular balance. Alongside this, a relatively sluggish response is triggered, where interocular mechanisms shift balance away from the deprived, assumedly degraded, eye, and toward the non-deprived, useful eye. This means that a paradigm designed to measure interocular balance over a wide range of deprivation durations should observe a transition, when the short-term system's response has saturated, and the long-term system's influence begins to dominate sensory eye balance; a biphasic effect. In the present study, we measure the effect of monocular deprivation (light-tight patching), over a period of 0.5 to 10 h, on dichoptic global motion coherence thresholds and monocular contrast sensitivity.

2. Methods

Participants. Seven participants, six naïve and one expert, between 20 and 35 years of age (6 female participants), with normal visual acuity, stereoacuity, and color vision[1], participated in the study. Prior to participation, participants performed a sighting test[2] to determine their preferred eye. All subjects gave informed consent and were compensated for their time as approved by the Institutional Review Board of the University of Massachusetts Boston.

The following sections on apparatus, tests of sensory eye balance are similar to and therefore taken from our previous publication (Ramamurthy and Blaser, 2018).

Apparatus. Ocular balance tasks were programmed using custom scripts in MATLAB (version R2015a), using Psychophysics Toolbox functions (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997). GMC and rivalry stimuli were presented on a calibrated 3D ASUS monitor with a resolution of 1080 × 1024. Dichoptic stimuli were presented using NVIDIA 3D Vision 2 LCD shutter goggles synchronized to the monitor with frames interleaved at 120 Hz and presented to each eye at 60 Hz. Unless otherwise specified, participants were seated 57 cm from the display in a quiet, dark room. Monocular qCSF measurements were made on a PF790 CRT monitor (resolution: 1024 × 768 @ 75 Hz) that had been linearized and fitted with a VideoSwitcher (Li & Lu, 2012) to expand grayscale bit depth from 8 to 16 bits.

Dichoptic Global Motion Coherence (GMC) tests. GMC stimuli were composed of a field of dots undergoing translational movement, presented within a visible rectangular aperture to aid binocular fusion. The aperture subtended 8 degrees of visual angle from a viewing distance of 57 cm. Dots were presented on a homogeneous gray background. Dots had a Weber contrast of 64% against a screen luminance of 12.5 cd/m^2 (as measured through the shutter goggles used for dichoptic presentation). The dot field consisted of 100 dots (each subtending 0.1 deg) with a (parametrically varied) proportion designated as *signal* dots with coherent, infinite lifetime translational motion. The remaining dots were designated as *noise* dots with a consistent, but random angle, motion vector. All dots drifted at 6 deg/s and were redrawn at a random location within the test window if they reached the aperture border. The two sets of dots were presented dichoptically, with signal dots in one eye and noise in the other (Fig. 1). GMC thresholds were measured using a single interval, direction discrimination task controlled by the PSI adaptive staircase procedure (Prins, 2012). On each (400 ms) trial, participants were asked to discriminate the global (coherence) direction of the dot field (left or right) and their response was recorded by a key press. Threshold values, then, reflect the proportion of signal dots that were required for direction discrimination, at 75% correct, for a particular participant and condition. The two dichoptic configurations (signal in left eye, noise in right; signal right, noise left) were mixed randomly within a block, for a total of 360 trials. A block took approximately 6 min to complete.

Monocular contrast sensitivity functions. Since short-term deprivation effects last for only about 20–30 min post patching (Lunghi et al., 2015; Zhou, Clavagnier, et al., 2013; Zhou et al., 2014) our assessment of the CSF had to be brief. We used the qCSF method - a procedure for rapid estimation of spatial CSFs that combines Bayesian adaptive inference with a trial-to-trial information gain strategy (Lesmes et al., 2010). The stimuli we used were adapted from Lesmes et al. (2010). Gabor stimuli (gaussian-windowed sinusoidal gratings) appeared with spatial frequencies ranging from 0.25 to 36 cpd, subtending 5.6° × 5.6° of visual angle, from a viewing distance of 128 cm. The gabor patches were either tilted 45° off vertical, to the left or right, and participants were asked to perform an orientation discrimination task. Gratings were presented for 120 ms and participants indicated right or left by pressing the corresponding arrow keys. A block consisted of 200 trials. We quantified pre- versus post-deprivation changes in the CSF using three parameters: CSF

[1] Stereoacuity was tested using a random dot stereogram 'Randot stereotest' (Stereo Optical Company) and color vision was screened using a Waggoner evaluation kit.

[2] This sighting dominance procedure is similar to that used by Mansouri et al. (2008) where participants, with both eyes open, looked through a sighting hole at a distant target. Participants closed and opened each eye in succession to determine the eye that was aligned with the target (Rosenbach, 1903). This eye was defined as the 'preferred eye' for this study.

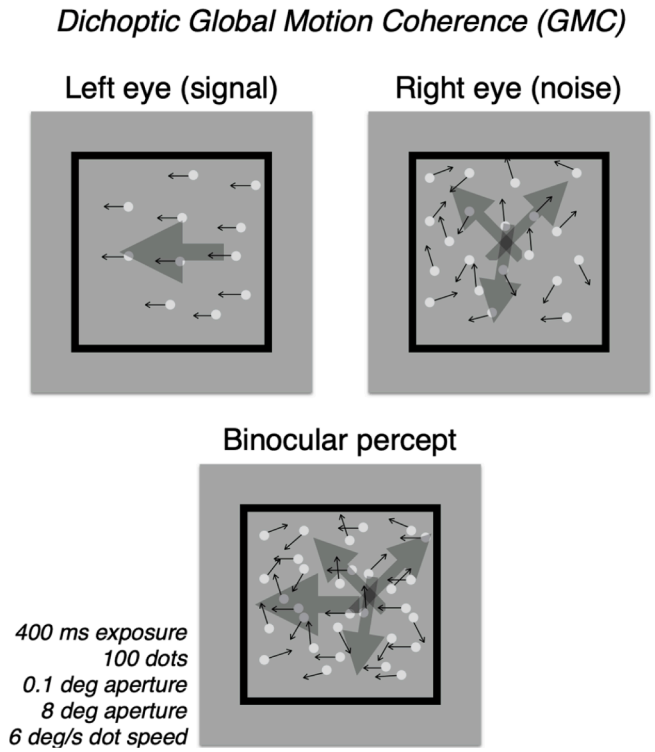

Fig. 1. Schematic of Global Motion Coherence (GMC) tests. In these tests, one eye receives a small set of coherently moving dots (signal, shown here in left eye) and the other, a large set of random-vector dots (noise, shown here in right eye). Images were interleaved dichoptically at 120 Hz. Which eye received signal or noise was randomized, trial to trial, as was the direction, left versus right, of the signal dots. The participant was instructed to indicate the direction of this motion with a keypress. An adaptive staircase was used to determine coherence thresholds (i.e. the proportion of signal dots required to achieve 75% correct direction judgements).

peak sensitivity ('gain'), area under the log CSF (AULCSF), and peak frequency (i.e. the spatial frequency at which there was peak sensitivity). Both eyes' thresholds were tested in mixed blocks. A block took approximately 6 min to complete.

3. Experimental procedures

Each participant was scheduled for a 10-hour session of deprivation during which participants wore a light-tight patch on their preferred eye. While many short-term deprivation studies have not shown any interaction with eye preference (Ramamurthy & Blaser, 2018; Zhou et al., 2014), some have shown larger effect sizes with deprivation of the preferred eye (Lunghi et al., 2011). Participants could engage in everyday activities during deprivation, but were restricted to the laboratory suite to ensure compliance and facilitate periodic testing. The main experiment consisted of a pre-deprivation baseline measure of ocular balance, followed by five intermittent testing points at 30, 150, 300, 450, and 600 min. The testing points consisted of the dichoptic GMC task followed by monocular qCSF tests, for a total of approximately 12 min.

Several days after the main experiment, two participants returned for testing. All procedures were the same as in the main experiments, except there were only two testing points (as opposed to six), the pre-deprivation baseline and a post-deprivation testing point after the full 10 h of deprivation. This *re-test* was conceived both as a modest internal replication, and as a way to sidestep any potential influence of the intermittent testing used in the main experiment.

4. Results

4.1. Deprivation duration effects on dichoptic global motion coherence thresholds (GMC)

We compared GMC thresholds from the deprived and the non-deprived eye at six different timepoints. The resulting laminar, well-separated functions for the non-deprived and deprived eye indicate a robust effect (Fig. 2a). A repeated measures ANOVA on these data with *deprivation duration* (0, 30, 150, 300, 450, and 600 min) and *deprivation state* (deprived or non-deprived) as factors showed a significant main effect of duration [$F(5,30) = 3.090$; $p = 0.023$; $\eta^2 = 0.034$] and state [$F(1,6) = 17.150$; $p = 0.006$; $\eta^2 = 0.42$] and a significant interaction [$F(5,30) = 7.004$; $p < 0.001$; $\eta^2 = 0.08$]. To facilitate comparison between measures, and to previous work (Ramamurthy & Blaser, 2018; Zhou, Clavagnier, et al., 2013), we then calculated normalized threshold ratios. For each participant and deprivation duration, an interocular ratio of thresholds was calculated (non-deprived eye/deprived eye), then normalized by the respective pre-deprivation ratio (Fig. 2b). This shows a net shift in interocular balance away from the non-deprived eye as a function of deprivation duration, with a turning point at 300 min (5 h) of deprivation. Normalized ratios from two participants that participated in the *re-test* experiment are shown for reference.

5. Deprivation duration effects on monocular contrast sensitivity

We then measured monocular contrast sensitivity functions (CSF) of the deprived and the non-deprived eye. We extracted three parameters from the qCSF (Lesmes et al., 2010): peak contrast sensitivity, area under the log CSF (AULCSF), and spatial frequency at peak sensitivity.

For peak contrast, the laminar, well-separated functions for the non-deprived and deprived eye indicate a robust effect (Fig. 2c). A repeated measures ANOVA on these data with *deprivation duration* (0, 30, 150, 300, 450, and 600 min) and *deprivation state* (deprived or non-deprived) as factors showed a significant main effect of duration [$F(5,30) = 2.87$; $p = 0.031$; $\eta^2 = 0.098$] and state [$F(1,6) = 74.2$; $p < 0.001$; $\eta^2 = 0.251$] and a significant interaction [$F(5,30) = 4.98$; $p = 0.002$; $\eta^2 = 0.115$]. For each participant and deprivation duration, an interocular ratio was calculated (non-deprived eye/deprived eye) then normalized by the respective pre-deprivation ratio (Fig. 2d). This shows a net shift in interocular balance away from the non-deprived eye as a function of deprivation duration, with a turning point at 300 min. Normalized ratios from two participants that participated in the *re-test* experiment are shown for reference.

For AULCSF, the laminar, well-separated functions for the non-deprived and deprived eye indicate a robust effect (Fig. 2e). A repeated measures ANOVA on these data with *deprivation duration* (0, 30, 150, 300, 450, and 600 min) and *deprivation state* (deprived or non-deprived) as factors showed a significant main effect of duration [$F(5,30) = 4.79$; $p = 0.002$; $\eta^2 = 0.125$] and state [$F(1,6) = 79.8$; $p < 0.001$; $\eta^2 = 0.181$] and a significant interaction [$F(5,30) = 15.70$; $p < 0.001$; $\eta^2 = 0.087$]. Normalized interocular ratios showed a net shift away from the non-deprived eye as a function of deprivation duration, with a turning point at approximately 150 min (Fig. 2e). Normalized ratios from two participants that participated in the *re-test* experiment are shown for reference.

We did not observe any shifts in spatial frequency tuning as a function of deprivation duration. A repeated measures ANOVA on these data with *deprivation duration* and *deprivation state* as factors showed no significant effect of duration [$F(5,30) = 0.617$; $p = 0.688$ $\eta^2 = 0.022$]. There was a significant effect of state [$F(1,6) = 18.9$; $p = 0.005$; $\eta^2 = 0.096$], but no interaction [$F(5,30) = 1.72$; $p = 0.160$; $\eta^2 = 0.056$]. Since the difference in spatial frequency tuning between the eyes (i.e., *state*) was present pre-deprivation, and not influenced by deprivation duration, it is likely unrelated to our experimental manipulations. It is worth

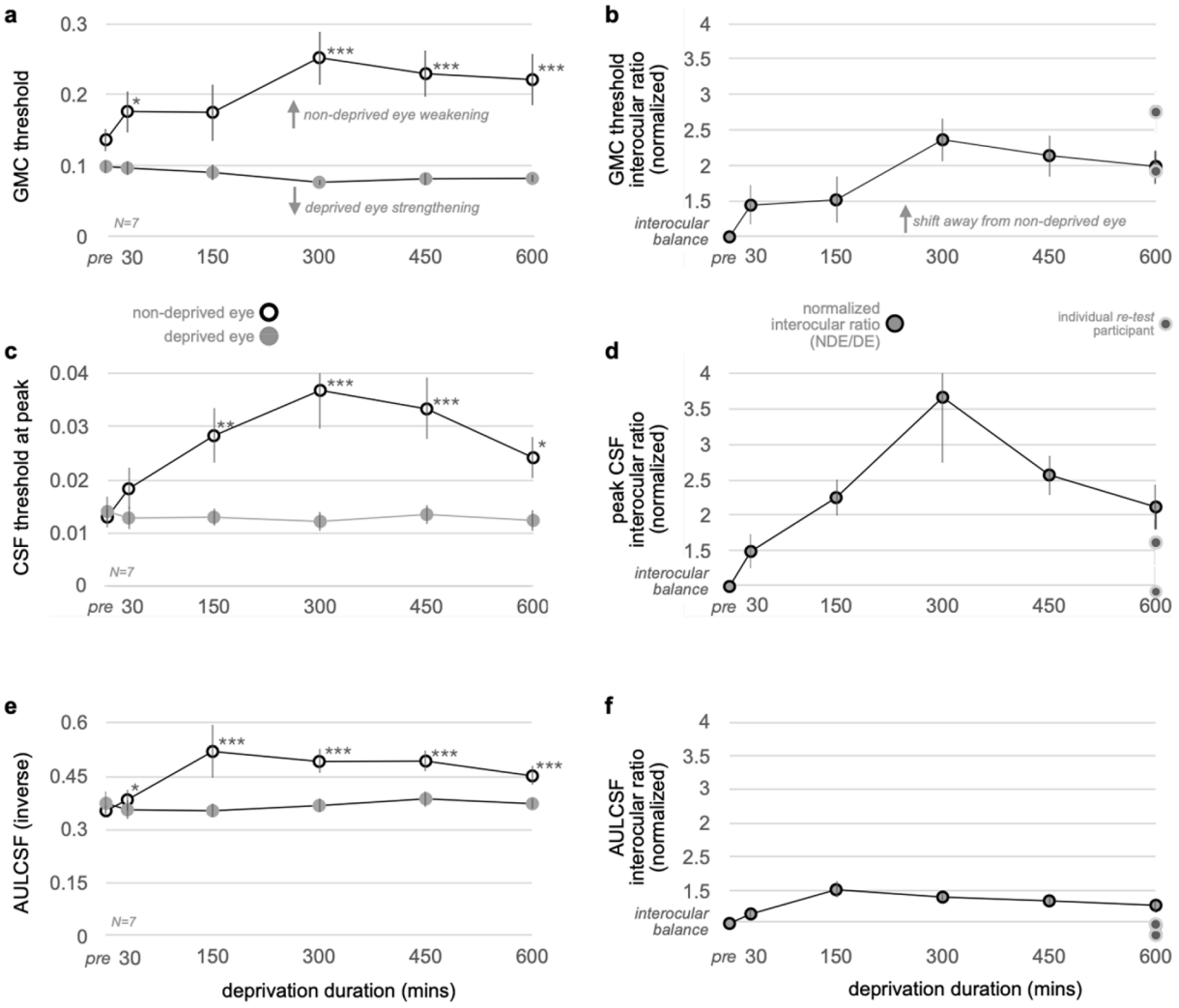

Fig. 2. Interocular balance changes as a function of monocular deprivation duration. The three panels on the left show thresholds (for GMC (a), CSF peak sensitivity (c), and AULCSF (e) tests, respectively) following monocular deprivation of up to 10 h, for both the non-deprived (open symbols) and deprived eyes (light-tight patched; filled symbols). Data points represent average values for all participants in the main experiment (N = 7; for separate participant plots, see Supplemental Materials Fig. 1). Error bars represent SEM. Within a particular test, we compared thresholds at each deprivation duration and for each eye (corrected for multiple comparisons) to pre-deprivation values ($p < 0.05$ (*), <0.01 (**), <0.001 (***)). Data from two participants that ran in the *re-test* are shown for reference. The three panels on the right show normalized interocular (non-deprived / deprived) threshold ratios (for GMC (b), CSF peak sensitivity (d), and AULCSF (f), respectively) and highlight the biphasic effect of deprivation duration on interocular balance, with an apparent turning point by 5 h.

noting again here that we patched the preferred eye of all participants: it seems that the preferred eye of our participants was, in general, tuned for slightly higher spatial frequencies (taken over all participants and deprivation durations (deprived mean [preferred eye] = 2.34 cpd, SD = 0.53; non-deprived Mean = 1.93 cpd, SD = 0.73).

6. Deprivation duration effects on the deprived eye versus the non-deprived eye

To evaluate the interaction effect between deprivation state and deprivation duration, we conducted post hoc tests comparing each measurement against pre-deprivation values. In this way, for each measure (peak CSF, AULCSF, and GMC thresholds), for each eye, we evaluated whether a particular deprivation duration significantly affected thresholds. We used an FDR method (Benjamini et al., 2006) to account for multiple comparisons (Glickman et al., 2014). In almost all cases (Fig. 2), deprivation significantly affected thresholds in the non-deprived eye. In contrast, changes in the deprived eye were not significant. We address this bias in effects in the *Discussion.*

7. Estimating the transition from short-term and long-term effects

Up until approximately 2.5–5 hrs of deprivation, our participants showed a shift in interocular balance away from the non-deprived, non-deprived eye, in tests both of GMC thresholds and monocular contrast sensitivity, consistent with short-term deprivation effects. After that, there was an apparent turning point, where increased deprivation duration started to shift balance in the other direction. Ten hours of deprivation, though, was not enough to see interocular balance restored, nor was it long enough to observe an actual reversal of the interocular ratio away from the *deprived* eye (i.e., a ratio < 1.0). As an exploratory exercise to provide testable predictions for future work, we used our data to estimate these two points.

We conducted a non-linear, bell-shaped repeated-measures regression (Motulsky & Christopoulos, 2004), over all participants' data from all three dependent variables (GMC threshold, peak sensitivity, and AULCSF). This analysis models a competition between two processes, one excitatory and the other inhibitory, with each captured by an underlying sigmoidal function; it is one of a class of biologically-plausible

"dose–response" models (Baldi & Bucherelli, 2005; Calabrese & Baldwin, 2001; Tuček et al., 2002). A bell-shaped regression has seven parameters, but four of these could be fixed, leaving three free parameters. The *starting plateau* was fixed at 1.0 to indicate a balanced interocular ratio, pre-deprivation. The *asymptotic plateau* was set to zero, to indicate a theoretical expectation of total dominance of the non-deprived eye, in the limit. The two *slope* parameters, which determine the steepness of the underlying excitatory and inhibitory responses (reflecting the two processes underlying the short- and long-term deprivation effects, respectively), respectively, were both fixed to a value of −1, a standard default for bell-shaped data (Motulsky, 2007). This left three free parameters. Two of these (*EC50_1* and *EC50_2*) modulate the time point at which the underlying excitatory and inhibitory processes, i.e. the short- and long-term deprivation effects, respectively, are at half-height. The final, *dip* parameter modulates the peak of the bell response.

Our goal was to fit the three data sets simultaneously, with *EC50_1* and *EC50_2* treated as shared parameters, and with the *dip* parameter left to vary between data sets (thereby allowing different measures to be differentially sensitive to deprivation). The regression considered each replicate as an individual point (N = 42 for GMC thresholds, peak sensitivity, and AULCSF data, respectively; N = 126 overall). As a first step, then, we tested whether the sharing of *EC50_1* and *EC50_2* was warranted. As expected, the extra-sum-of-squares F test could not reject the null hypothesis that these parameters were the same for all data sets ($F(4,117) = 0.321$; $p = 0.864$). In the final fit ($S_e = 0.80$), the values for the two shared parameters were *EC50_1* = 390 and *EC50_2* = 391. The unshared *dip* parameters for GMC threshold, peak sensitivity, and AULCSF were 1434, 2036, and 800, respectively (the differences in the dip parameter reflects the underlying differences in the sensitivity of the measures to deprivation).

We then compared this model to a null hypothesis that monocular deprivation had a monotonic effect on the interocular ratio (i.e., that there were no separate short- and long-term processes, but just one process that shifts balance away from the non-deprived eye, asymptotically, as a function of deprivation duration), which we modeled as plateaued exponential growth. This model had three parameters, *Y0* (the starting point of growth, which was fixed at an interocular ratio of 1.0), *k* (controlling growth rate, which was a shared parameter for all three data sets), and *YM* (the plateau of growth) which was left as a free parameter to allow for the three data sets to have different asymptotes. After fitting, $k = 0.0121$, and *YM* was equal to 2.08, 2.73, and 1.39 for GMC, peak CSF, and AULCSF, respectively. Since the bell-shaped and exponential plateau models were not nested, an extra-sum-of-squares F test was not appropriate, so we conducted an AIC (Akaike's Information Criterion) model comparison. The probability that the exponential plateau model was correct was 30.6%, while that for the bell-shaped model was 69.4%, yielding a ratio of 2.27 in favor of the bell-shaped model.

Given that the bell-shaped model was preferred, we then used it as planned to generate estimates, for each of the three measures, of two points of interest: a *balance point* (an estimate of the number of hours of deprivation until binocular balance is restored, i.e., an interocular ratio of 1.0), and a *reversed-shift* point (an estimate of the number of hours of deprivation until interocular balance shifts substantially away from the *deprived* eye which we specified to be an interocular ratio of 0.5, commensurate, but opposite, to an interocular ratio of 2.0). For GMC threshold measures, the model predicted the *balance point* would be reached at 35.7 h (95% CI: 15.8 to 98.1) (Fig. 3). In other words, it is predicted that it would take approximately 1.5 days of continuous deprivation for the long-term effect to cancel out the short-term effect. The model predicted a *reversed-shift* of 84.0 h (CI: 23.6 to 224.3), or approximately 3.5 days of continuous deprivation, to observe a robust shift in interocular balance away from the deprived eye. For CSF peak sensitivity, the model predicted a *balance point* of 53.5 h (2.2 days) (CI: 20.2 to 140.9) and a reverse-shift of 118.9 h (5.0 days) (CI: 28.5 to 308). For the AULCSF, the balance point was 17.1 h (CI: 8.4 to 52.7) and *reverse-shift* was 47.5 h (2.0 days) (CI: 16.4 to 135.5).

8. Discussion

We used (up to) 10 h of light-tight monocular deprivation to induce shifts in interocular balance. We found a biphasic effect as a function of deprivation duration on both dichoptic global motion coherence thresholds (GMC) and monocular contrast sensitivity (we did not observe any deprivation-induced effects on spatial frequency tuning). Consistent with recent reports of short-term deprivation effects (Lunghi et al., 2011; Ramamurthy & Blaser, 2018; Zhou, Clavagnier, et al., 2013; J. Zhou et al., 2015), we initially observed a post-deprivation shift in interocular balance away from the open, non-deprived eye. This effect increased as a function of deprivation duration over a period of approximately 5 h. We then observed a turning point: more deprivation time did not serve to further increase the effect, but reduce it. To our knowledge, this is the first time a biphasic effect of monocular deprivation on ocular dominance plasticity has been observed in typical adult humans.

However, nearly 50 years ago, there was a group that tested the

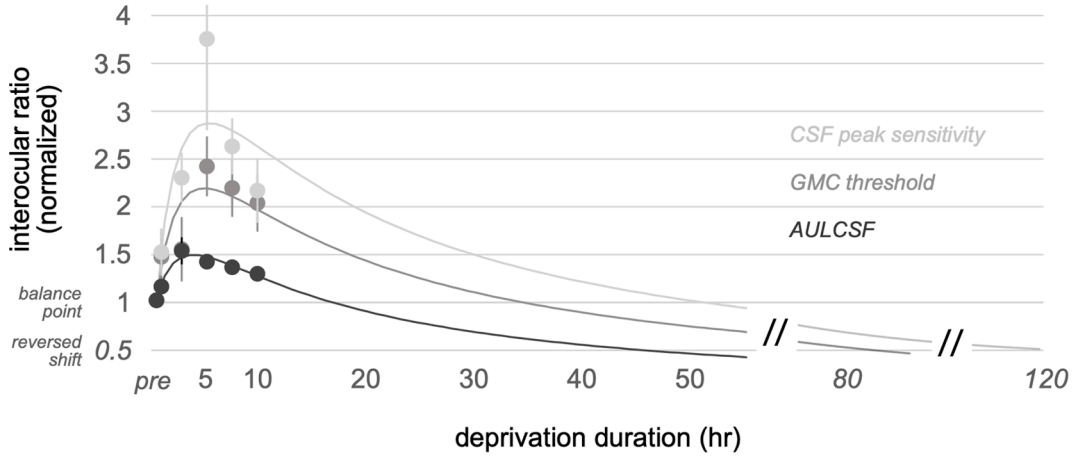

Fig. 3. Biphasic regression model for GMC thresholds, peak contrast sensitivity, and AULCSF as a function of deprivation duration. All participants' data (N = 7) from all three measures (replotted here from Fig. 2 b/d/f) were fit ($S_e = 0.80$) by a common bell-shaped dose response model (the null hypothesis of a monotonic, plateaued exponential was rejected) with one free parameter for each measure, modulating the peak effect. As an exploratory analysis, extrapolated fits were used to estimate two points of interest: a *balance point*, reflecting a prediction of when interocular balance would be restored, and a *reversed-shift point*, a prediction of the deprivation duration required for a robust reversal (to 0.5) of the interocular ratio.

effect of up to *two weeks* of monocular deprivation on monocular critical flicker frequency thresholds. Consistent with our results, Zubek & Bross (1972), Zubek and Bross (1973a) found an initial decrease in the critical flicker frequency (CFF) threshold in the non-deprived eye (i.e., a weakening), followed by an increase in the CFF in that eye (estimating from the two studies, the total delta from decrease to increase was approximately 3–4 flash/s, or just under a 10% change from a starting CFF of 40–41 flash/s). The transition from weakening to strengthening of the non-deprived eye occurred at the 6–9 h mark, not far off from our present finding of 5 h. Zubek's work though was controversial: coercive to its subjects, and seen as facilitating the development of sensory deprivation as a form of torture (Raz, 2013). After publication of back-to-back studies in *Science* (Zubek & Bross, 1972) and *Nature* (Zubek and Bross, 1973a), this line of inquiry was abandoned by the field, and Zubek died soon after, of a probable suicide (Raz, 2013). While this work has not been cited in recent studies on monocular deprivation, it certainly presages it. That said, these studies did have critical limitations, including testing with only a monocular measurement (as opposed to including inherently interocular measures such as dichoptic GMC, binocular phase combination, and rivalry), and the fact that they did not observe any effects with 'diffuser' deprivation (i.e. flooding an eye with unpatterned light, usually through fitting a translucent lens) (Zubek and Bross, 1973b). This latter finding is incompatible with recent work showing both that diffuser deprivation (Lunghi et al., 2011; Zhou, Clavagnier, et al., 2013) and many other forms of deprivation - even those that preserve gross luminance, and color such as low-pass filtering (Zhou et al., 2014) or kaleidoscopic image fractionation (Ramamurthy & Blaser, 2018) – induce effects comparable to light-tight patching.

9. Deprivation effects in the deprived versus non-deprived eye

Here we found a significant deprivation effect in the non-deprived eye, for all three measures, but no significant effect in the deprived eye. While our previous work showed evidence for reciprocal effects, in monocular CSF tests, effects were smaller in the deprived eye (Ramamurthy & Blaser, 2018). It is challenging to fully evaluate eye-specific effects in the literature, because most studies either report only interocular ratios, or employ only inherently push–pull tests (such as rivalry or binocular phase combination). In either case, it is ambiguous whether an observed shift in balance is due to a change in the deprived eye, the non-deprived eye, or both. There is very little data from purely monocular tests following deprivation, and these results are mixed. Zhou, Thompson, et al. (2013), Zhou et al. (2017), Zhou, Clavagnier, et al. (2013) have measured monocular contrast thresholds in a handful of observers (following 150 min of deprivation) and observed a threshold increase in the non-deprived eye and a reciprocal decrease in the deprived, but, while effects were present in both eyes, there was no direct comparison, so it is difficult to assess bias. Lunghi et al. (2011, supplemental materials) measured contrast detection thresholds (following 150 min of deprivation) and found an increase in threshold in the non-deprived eye, and no effect in the deprived. Taking a different tack, Chadnova, et al. (2017) measured monocular deprivation effects based on MEG power (of frequency tagged signals in primary visual cortex) and found reciprocal effects, but with a much more robust effect in the deprived eye (effects in the non-deprived eye only reached significance at one of four post-deprivation testing points, in a light-tight patch condition, and did not reach significance at any time point in a translucent patch condition). Taken together then, there is only one thing that can be said with certainty: short-term monocular deprivation weakens the non-deprived eye and/or strengthens the deprived.

In long-term monocular deprivation with adult humans, while we see the expected, complementary pattern (i.e., that long-term monocular patching strengthens the non-deprived eye and/or weakens the deprived), again there is little work that bears on bias. Shibata, et al. (2012) found that after 3 days of deprivation, while there were no immediately evident deprivation effects on monocular contrast detection thresholds (in either eye), there was a greater increase in plasticity, i.e. a relative strengthening, of the non-deprived eye, versus the deprived eye (as measured by changes in contrast detection thresholds in a perceptual learning regime). After two days of monocular deprivation, Lou et al. (2011) concluded that cortical excitability, as measured by the perception of TMS-induced phosphenes, was reduced in both hemispheres symmetrically. In their critical flicker frequency tests, following days or weeks-long deprivation, Zubek & Bross (1972), Zubek and Bross (1973a) found an improvement in the non-deprived, but not the deprived, eye.) There has been some related work in long-term monocular deprivation in adult, animal models. In general, the animal literature tracks very closely to the human literature in terms of the basics of ocular dominance plasticity, including the neural and behavioral consequences of deprivation and the interaction with development (Dahlhaus & Levelt, 2010). After maturation of the visual system in adult animals, as in humans, the effects of long-term (several days) deprivation are more modest, and with evidence of reciprocal effects on eyes, but here too some evidence for bias can be found, with more pronounced effects in the non-deprived eye (Hofer et al., 2006; Sato & Stryker, 2008; Tschetter et al., 2013).

It is difficult to determine the source of eye-bias in deprivation effects (short-term, or long-term) currently, since they have been inconsistent in previous work, and there has been no direct attempt to characterize them. We can only speculate that biases may be exposed, or induced, by the particulars of the deprivation duration and type (e.g. light-tight or translucent), and the particulars of the testing session itself, including the type of tests (e.g., measuring effects on perceived, suprathreshold contrast stimuli versus contrast thresholds, or measuring effects on a full CSF versus effects at a particular frequency), how long after deprivation tests are initiated, and how long they take. In animal models as well, this complex interplay between affected eyes (and the interaction with development) is not yet well understood (Sawtell et al., 2003), but is thought to reflect the action of opposing, mutually-regulating Hebbian and homeostatic mechanisms in visual cortex (Keck et al., 2017; Mrsic-Flogel et al., 2007; Turrigiano & Nelson, 2000, 2004; Whitt et al., 2014).

10. Future work with yet longer-term deprivation

The maximum deprivation duration of 10 h in the present study was sufficient to see a turning point in ocular dominance plasticity, but not a restoration of balance (or, further, a reversal of the interocular ratio). Since we could not observe them directly, we extrapolated a biphasic (bell-shaped) dose-response model of our data to estimate these points. Our predictions indicated that for dichoptic global motion coherence, for instance, the short-term and long-term responses should cancel out, restoring interocular balance, after about 36 h of deprivation. A robust reversal, away from the deprived eye, was estimated at 84 h (3.5 days) of deprivation.

It is important to be clear about the limitations of this exercise. While providing testable predictions for future work, our estimates are underspecified by the data, as evidenced by large confidence intervals, and should be treated with caution. Even with a dedicated study that could extend the deprivation times sufficiently, recovery or reversal may never be reached. Given the only modest effects of even two weeks of deprivation from Zubek & Bross' controversial work (1973a), and the conventional wisdom that patching interventions for amblyopia in adult humans may have only limited effect (for a review, see Holmes & Levi (2018)), there is reason to be pessimistic. Additionally, while the predictions for the balance and reversal points differed for the three measures, confidence intervals were so large that it is not possible to reject the (more parsimonious) null hypothesis that these points may actually be common across the measures. This would, in fact, be our hypothesis for future work: while effect sizes would certainly vary depending on how sensitive a particular psychophysical measure is to interocular balance, the *turning*, *balance*, and *reversed-shift* points would be shared. This seems reasonable, as the underlying mechanism that drives these

effects (assumedly, interocular gain control) is common, independent of the particular test used to assess it. Finally, while the bell-shaped regression model has biological plausibility (Baldi & Bucherelli, 2005; Calabrese & Baldwin, 2001; Tuček et al., 2002), we employed it primarily as a data flitting method. We fully expect a future, dedicated treatment to supplant it with a model that incorporates processes thought to be involved in short- and long-term deprivation effects, likely emerging from formal models of interocular gain control (Ding et al., 2013; Ding & Sperling, 2006).

Ultimately, we argue here that the biphasic nature of interocular balance shifts as a function of deprivation reflect two opposing processes that act at different timescales. Upon deprivation, when the visual information from one eye is removed (for instance through light-tight patching as in the present work), reduced (through, for instance, diffuser deprivation), or manipulated in a way that leads to its suppression (for instance, reducing its usefulness to active vision, as in kaleidoscopic deprivation (Ramamurthy & Blaser, 2018)), the visual system leverages interocular gain control mechanisms to downweigh the non-deprived eye and/or potentiate the deprived eye in a homeostatic effort (Fox & Stryker, 2017) to restore interocular balance prior to binocular combination. Then, as deprivation continues, a relatively sluggish system, noting the persistent lack of utility of one monocular stream, begins a process of downweighting it and/or potentiating the non-deprived eye. During development, this latter process leads to extreme outcomes, including permanent changes to neural representation and visual processing (Sengpiel & Blakemore, 1996). In an adult system, consequences are likely more modest (Morishita & Hensch, 2008; Sato & Stryker, 2008), but further work with yet longer-term deprivation is necessary to reveal the full trajectory of the ocular dominance shift.

CRediT authorship contribution statement

Mahalakshmi Ramamurthyi: Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing - original draft, Visualization, Investigation. **Erik Blaser:** Supervision, Resources, Project administration, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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