Correspondences

Dichoptic training enables the adult amblyopic brain to learn

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Adults with amblyopia, a common visual cortex disorder caused primarily by binocular disruption during an early critical period, do not respond to conventional therapy involving occlusion of one eye [1]. But it is now clear that the adult human visual cortex has a significant degree of plasticity [2], suggesting that something must be actively preventing the adult brain from learning to see through the amblyopic eye. One possibility is an inhibitory signal from the contralateral eye that suppresses cortical inputs from the amblyopic eye [3,4]. Such a gating mechanism could explain the apparent lack of plasticity within the adult amblyopic visual cortex [5,6]. Here we provide direct evidence that alleviating suppression of the amblyopic eye through dichoptic stimulus presentation induces greater levels of plasticity than forced use of the amblyopic eye alone. This indicates that suppression is a key gating mechanism that prevents the amblyopic brain from learning to see.

Eighteen adults with amblyopia were trained on an engaging video game (Tetris) presented on head-mounted video goggles for one hour per day over two weeks. Nine patients played the game monocularly with the fellow eye patched. The remaining nine patients played the same video game dichoptically, whereby stimulus elements were presented separately to each eye and lower contrast stimuli were presented to the fixing eye to counteract suppression and allow for binocular combination [7]. After two weeks, the participants in the group who were trained monocularly were crossed over to the dichoptic condition.

Dichoptic training resulted in significantly greater learning effects than monocular training (Figure 1). Both groups showed significant improvements in visual acuity (dichoptic $t_8 = 12.4$, $p < 0.0001$, monocular $t_8 = 2.5$, $p = 0.04$), but dichoptic learning led to significantly greater improvements than monocular learning (greater than a factor of 4; $F_{1,16} = 41.5$, $p < 0.0001$; Figure 1A). When the monocular group were crossed over to dichoptic training, there was a pronounced (over a factor of 4) and significant further improvement in visual acuity ($t_8 = 13.1$, $p < 0.0001$).

Dichoptic training also resulted in significantly greater improvements in stereopsis than monocular training ($F_{1,13} = 8.4$, $p = 0.01$; Figure 1B). Dichoptic training improved stereopsis by a factor of 4 ($t_5 = 3.1$, $p = 0.03$) while monocular training had no significant effect ($t_8 = 1.5$, $p = 0.2$). When the monocular group was crossed over to dichoptic training, a sizeable (factor of 4) and significant ($t_8 = 2.8$, $p = 0.02$) improvement in stereopsis occurred. In addition, dichoptic training resulted in a large (over a factor of 4) and significant ($t_8 = 7.7$, $p < 0.0001$) reduction in suppression as quantified by our dichoptic contrast balancing procedure [8]. This was significantly greater than the effect of monocular training ($F_{1,16} = 29.6$, $p < 0.0001$; Figure 1C), which did not significantly reduce suppression ($t_8 = 1.8$, $p = 0.2$). When the monocular group was crossed over to dichoptic training, a significant reduction in suppression occurred (factor of 2, t8 = 2.8, p = 0.02). Five patients attended a three month follow-up and their improvements remained stable.

It has been reported that 40 hours of monocular video game play can improve visual acuity in adults with amblyopia by an average of 1.6 LogMAR, whereas performing other monocular activities has no effect [9]. This may be due to attentional or motivational effects associated with video game play [10]. Our results demonstrate that effects of the same or larger magnitude can be achieved after just 10 hours of dichoptic videogame play and that dichoptic training is much more effective than monocular training. This strongly suggests that suppression of the amblyopic eye gates plasticity within the adult amblyopic visual cortex. By directly reducing suppression (Figure 1C), learning was enabled and significant

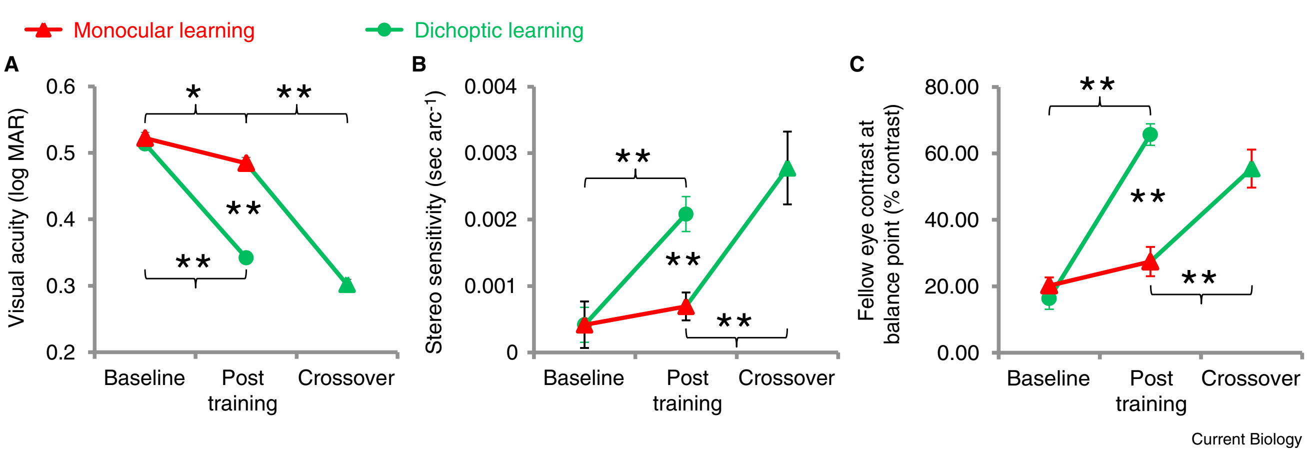

Figure 1. Improvements in visual function after monocular vs. dichoptic training.
Red lines depict monocular training, green lines depict dichoptic training. Note that the group trained monocularly was crossed over to dichoptic training after two weeks. (A) Improvements in amblyopic eye visual acuity (LogMAR units). (B) Improvements in stereopsis (stereo sensitivity, sec arc^{-1}). (C) Reductions in interocular suppression (%contrast tolerated in the fellow eye when the amblyopic eye views a 100% contrast stimulus). Asterisks denote statistical significance (* = p < 0.05, ** = p < 0.001) and error bars show within-subjects standard error of the mean.

improvements in both monocular and binocular visual function occurred (Figure 1A,B), although visual function did not recover to normal levels. This provides a basis for the treatment of amblyopia in adults who currently have no treatment options.

Supplemental Information

Supplemental Information includes experimental procedures, supplemental results, supplemental references and one table and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2013.01.059.

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Conflict of interest

Authors R.F.H. and B.T. are inventors in an issued patent owed by McGill University, and may receive financial benefit should McGill University decide to commercialize.

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A push-pull treatment for strengthening the 'lazy eye' in amblyopia

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Almost all individuals exhibit sensory eye dominance, one neural basis of which is unequal interocular inhibition. Sensory eye dominance can impair binocular functions that depend on both excitatory and inhibitory mechanisms [1–3]. We developed a 'push-pull' perceptual learning protocol that simultaneously affects the excitatory and inhibitory networks to reduce sensory eye dominance and improve stereopsis in adults with otherwise normal vision [4]. The push-pull protocol provides a promising clinical paradigm for treating the extreme sensory eye dominance in amblyopia ('lazy eye'). The prevailing standard of care does not directly treat sensory eye dominance; instead, selected excitatory functions in the amblyopic eye are stimulated while the strong eye is patched, on the assumption that recovery of the weak eye's excitatory functions rebalances the eyes. Patching the strong eye does not directly address interocular inhibition; in contrast, the push-pull protocol by design excites the weak eye, while completely inhibiting the strong eye's perception to recalibrate the interocular balance of excitatory and inhibitory interactions. Here, we show that three adult amblyopes who trained on the push-pull protocol gained longstanding improvements in interocular balance and stereopsis. Our findings provide a proof-of-concept and evidence that push-pull learning leads to long-term plasticity.

During the push-pull training, attentional cueing causes the rivaling half-image at corresponding retinal points in the amblyopic eye to be perceived (push), while the half-image in the strong eye is perceptually suppressed (pull) (Figure 1A). We measured relative sensory eye dominance (with binocular rivalry stimulus), monocular contrast threshold and stereoacuity ([3,4]; Supplemental Information) in the pre-training and post-training phases to reveal the learning effects (pre *versus* post). The observers were retested 4–8 months after the training ended for evaluation of learning retention (pre *versus* retain).

Figure 1B(i) shows the weak eye's balance contrast reduces significantly post-training, indicating increased strength of the amblyopic eye's channel (S1: $t(8) = 3.089$, $p < 0.015$; S2: $t(8) = 12.703$, $p < 0.001$; S3: $t(8) = 4.895$, $p = 0.001$). The learning effect is retained (S1: $t(8) = 3.531$, $p < 0.008$; S2: $t(7) = 7.655$, $p < 0.001$; S3: $t(8) = 4.215$, $p < 0.003$). The strong eye's balance contrast increases significantly post-training for observers S1 ($t(8) = –5.520$, $p = 0.001$) and S3 ($t(8) = –9.163$, $p < 0.001$), and the learning effect is retained (S1: $t(8) = –4.169$, $p = 0.003$; S3: $t(8) = –5.036$, $p = 0.001$). For observer S2, the increase in the strong eye's balance contrast is insignificant ($t(8) = –1.341$, $p = 0.217$) and remains unchanged during retention testing ($t(7) = –0.701$, $p = 0.506$). The relative sensory eye dominance significantly reduces post-training (S1: $t(8) = 4.632$, $p = 0.002$; S2: $t(8) = 12.321$, $p < 0.001$; S3: $t(8) = 10.420$, $p < 0.001$), and the learning effect is retained (S1: $t(8) = 4.960$, $p = 0.001$; S2: $t(7) = 7.940$, $p < 0.001$; S3: $t(8) = 6.047$, $p < 0.001$) (Figure 1B(ii)). These findings reveal that the push-pull training improves interocular balance and induces a sustained learning effect.

Figure 1B(iii) shows the training significantly reduces the amblyopic eye's contrast threshold for observers S1 ($t(6) = 3.032$, $p = 0.023$) and S2 ($t(6) = 2.553$, $p = 0.043$), with significant retention for S1 ($t(6) = 3.732$, $p = 0.010$) but not S2 ($t(6) = 1.377$, $p = 0.218$). The reduced contrast thresholds in S1 and S2 cannot entirely account for the changes in sensory eye dominance. The learning effect for S3 is insignificant ($t(6) = 1.901$, $p = 0.106$) and remains unchanged during retention testing ($t(6) = 1.559$, $p = 0.170$). For all observers, the strong eye's contrast threshold remains unchanged ($p > 0.05$). Notably, the improvement in the weak eye mirrors that by others who exclusively train the amblyopic eye, with the main goal of improving