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Amblyopia and the binocular approach to its therapy

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ABSTRACT

There is growing evidence that abnormal binocular interactions play a key role in amblyopia. In particular, stronger suppression of the amblyopic eye has been associated with poorer amblyopic eye visual acuity and a new therapy has been described that directly targets binocular function and has been found to improve both monocular and binocular vision in adults and children with amblyopia. Furthermore, non-invasive brain stimulation techniques that alter excitation and inhibition within the visual cortex have been shown to improve vision in the amblyopic eye. The aim of this review is to summarize this previous work and interpret the therapeutic effects of binocular therapy and non-invasive brain stimulation in the context of three potential neural mechanisms; active inhibition of signals from the amblyopic eye, attenuation of information from the amblyopic eye and metaplasticity of synaptic long term potentiation and long term depression.

1. Introduction

Amblyopia therapy is a large area as many different treatments have been proposed over the last 100 years. One promising approach for the treatment of adults with amblyopia is the combination of patching and perceptual learning in its many varied forms, for which both monocular and binocular benefits have been documented. More recently, the focus of research in this area has shifted from monocular interventions that involve patching of the fellow eye to approaches that directly target binocular visual function and as the primary therapeutic step. The emerging field of binocular approaches to amblyopia therapy is the topic of this review.

It is accepted that abnormal binocular visual experience in early childhood causes amblyopia and that suppression (typically measured using the worth 4 dot test) plays an important part of the clinical diagnostic picture. It has also been shown that loss of binocularity is one of the defining features of amblyopia (McKee, Levi, & Movshon, 2003) However the potential importance of binocular approaches to amblyopia therapy has only recently received widespread attention (Birch et al., 2014; Cleary et al., 2009; Hess, Mansouri, & Thompson, 2010; Hess, Thompson, & Baker, 2014; Hess et al., 2014; Li, Thompson, et al., 2013; Li et al., 2014; Mansouri et al., 2014; Ooiemail, Su, Natale, & He, 2013; Spiegel, Li, et al., 2013; To et al., 2011). This has led to increased interest in the development of amblyopia treatments that directly address binocular dysfunction by promoting binocular vision and reducing inhibitory interactions within the visual cortex. In this review, we first summarize emerging approaches to the treatment of amblyopia that emphasize binocular visual function. We then describe the relationship between suppression of the amblyopic eye and the depth of amblyopia and explore whether suppression is due to active inhibition of information from the amblyopic eye or is simply the result of attenuated amblyopic eye signals. The concept of metaplasticity is then introduced and applied to the recovery of visual function in amblyopia. Finally, the results of studies into the application of non-invasive visual cortex stimulation to amblyopia are summarized and placed in the context of inhibition, attenuation and metaplasticity.

2. Emerging treatment options for amblyopia

Patching therapy has been used to treat amblyopia for hundreds of years even though its shortcomings are many; compliance is poor (Searle et al., 2002) because of the social and psychological difficulty of forcing a child to wear a patch combined with the impaired vision experienced by the child when the patch is in place (Holmes et al., 2003; Webber et al., 2008). Although 79% of children show at least a 2 line improvement after 4 months of patching (Repka et al., 2003), 25% of these children will regress to some degree once the patch is removed (Holmes et al., 2004). More

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importantly, the binocular outcome is often poor regardless of the improved amblyopic eye acuity (Birch, 2012). One reason for this is likely to be the nature of the viewing conditions during patching (i.e. monocular) compared with those after patching, namely binocular viewing. We do not yet know how patching works, although possible mechanisms include a reduction of interocular suppression or a purely monocular improvement in the processing of signals from the amblyopic eye. Since there is such a poor binocular outcome from patching, it may be safe to conclude that the effects of patching primarily involve monocular mechanisms.

There have been a number of suggestions for improving the therapeutic approach to amblyopia. Some of these are purely monocular, some are monocular under otherwise binocular conditions and one is purely binocular, involving dichoptic stimulation and a dichoptic manipulation of contrast to enable simultaneous use of both eyes. A summary of different treatment suggestions is shown in Fig. 1. The first attempt to provide the combination of short-term occlusion (20 min), controlled visual stimulation and attentive game play (noughts and crosses) was the CAM treatment (Campbell et al., 1978). Its beneficial effects were later isolated to the short term nature of the occlusion and the attentive game play (Mitchell, Howell, & Keith, 1983). Another step in terms of the monocular approach was Neurovision in which perceptual learning for threshold detection was combined with short-term patching (Bonneh, Sagi, & Polat, 2004; Polat et al., 2004, 2005). There is no doubt that perceptual

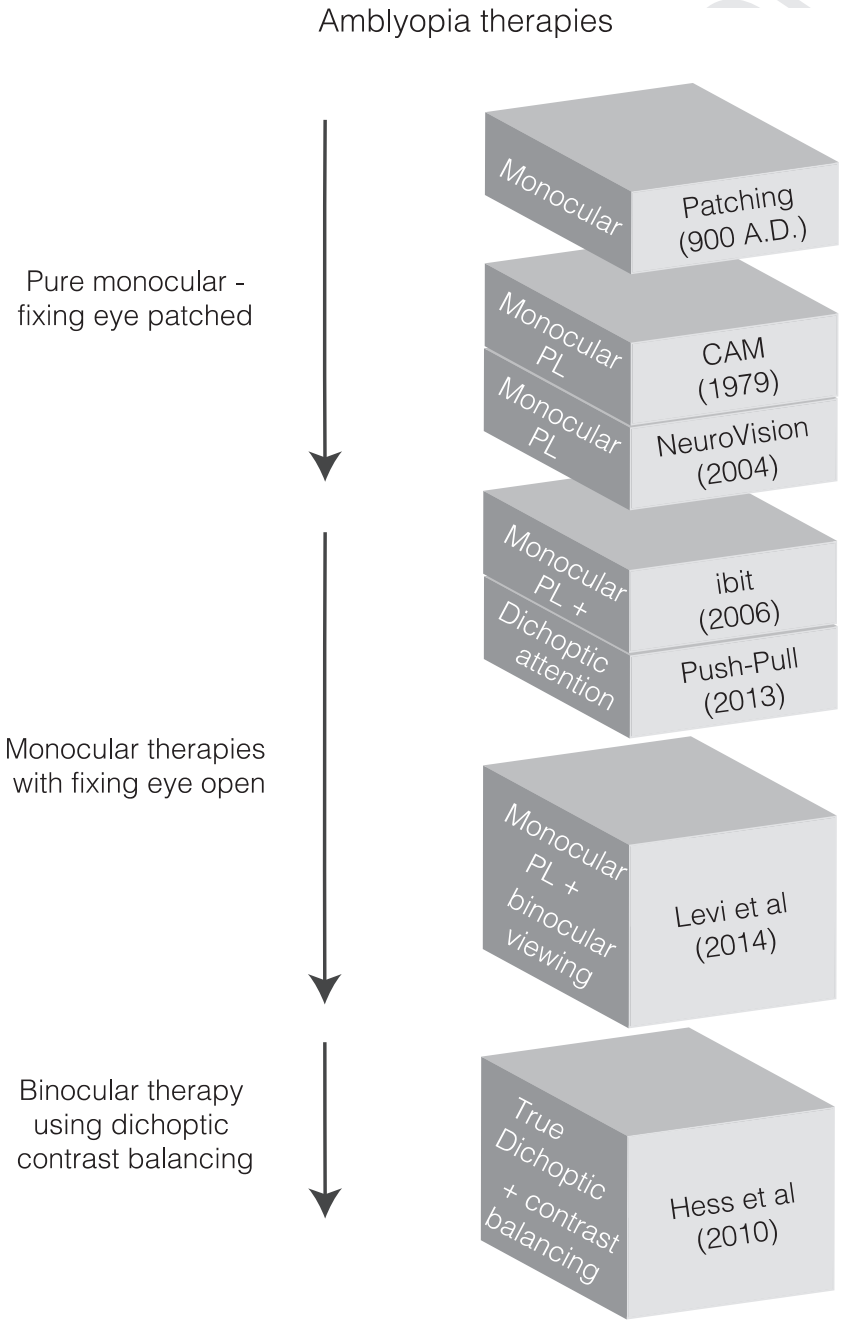

Fig. 1. A summary of different principled approaches to the treatment of amblyopia, some purely monocular, some containing a binocular element and others purely binocular with dichoptic manipulation of parameters. Because the literature on monocular perceptual learning is large, only representative examples are shown. Also, there are a number of behavioral optometric approaches (Press, 1981) that are not included as these are beyond the scope of this review.

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learning combined with short-term patching is much better than longer-term patching with passive stimulation in terms of improving monocular acuity (Li et al., 2005), however its usefulness for re-establishing binocular vision and stereopsis is less clear. A number of hybrid-binocular approaches have been suggested, which are all directed to recovering monocular function but rather than doing this under monocular conditions they do it under binocular viewing. The aim is to involve the fixing eye in recovery of vision through intensive training/detection of targets presented exclusively to the amblyopic eye. These approaches are not designed to reduce suppression, strengthen fusion and re-establish binocular vision. The iBit system (Cleary et al., 2009), the "Push–Pull" (Ooiemail et al., 2013) and the recent gaming approach by Noah et al., 2014 (Fig. 1) fall into this category. An altogether different principle was introduced by Hess, Mansouri, and Thompson (2010) (Fig. 1). In this approach the primary aim is to restore binocular fusion and stereopsis with an expected secondary consequence of improved vision of the amblyopic eye. To achieve this, complementary dichoptic stimuli are used such that the visual task can only be solved if both left and right information eye is combined (the binocular criterion). To achieve this, the contrast of the signal seen by the fixing eye is reduced (to negate suppression) to a point where binocular combination is achievable. This "balance point" is determined individually for each patient. Over time, the treatment strengthens and extends the contrast range over which binocular fusion can occur until it includes images of the same contrast in each eye (comparable to natural viewing). There are no circumstances under which the treatment becomes monocular because without binocular combination, the visual tasks used for treatment are impossible. This approach is based on the theory that the amblyopic visual system retains the capacity for binocular function and that suppression of the amblyopic eye plays an important role in both the binocular and monocular functional losses associated with amblyopia. It is important to note that Evidence to support this theory is outlined below.

3. Clinical suppression

Clinical suppression refers to the lack of contribution of an amblyopic and/or strabismic eye under binocular viewing conditions. The most common tool for assessing this clinically is the worth 4 dot test in which stimuli of different colors are presented anaglyphically and the degree to which each eye contributes to perception is assessed subjectively. This allows for the diagnosis of suppression and for it to be categorized as mild or severe. Although there have been a variety of more quantitative procedures suggested (Zhou, Huang, & Hess, 2013) there is no gold standard for suppression measurement and in fact it is currently not an important part of the standard clinical assessment. For this reason, the relationship between clinical suppression and the degree of amblyopia has, until recently, not been known. One of the first attempts to address this question was a laboratory study conducted by Holopigian, Blake, and Greenwald (1988). Their sample was small ($n = 9$) and it included patients with anisometropic amblyopia, strabismic (esotropic) amblyopia and alternating strabismus with no amblyopia. They reported an inverse relationship between acuity and depth of suppression, which they quantified in terms of contrast (weaker suppression was associated with poorer acuity).

More recently, new approaches have been developed to quantify the degree of suppression and these have been applied to larger samples of patients with amblyopia. They all come to a similar conclusion, namely that there is a direct relationship between the strength of suppression and the depth of amblyopia. Fig. 2 shows pooled data for 106 patients with amblyopia from three recent

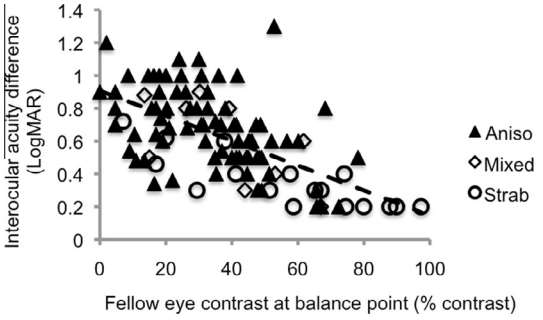

Fig. 2. The relationship between contrast in the fellow fixing eye at the balance point (suppression) and acuity difference between the eyes ($n = 106$). *Dashed line*: the best linear fit to the data. The relationship shows that the lower the balance point contrast in the fellow fixing eye (i.e., the greater the difference in contrast between the eyes required for binocular function indicating stronger suppression; smaller values on the *X*-axis), the greater the difference in acuity between the two eyes (larger values on the *Y*-axis). Data from (Li, Hess, et al., 2013; Li, Thompson, et al., 2013; Li et al., 2011).

studies (Li, Hess, et al., 2013; Li, Thompson, et al., 2013; Li et al., 2011) where the degree of suppression measured using a dichoptic motion coherence task (Mansouri, Thompson, & Hess, 2008) is plotted against the interocular LogMar acuity difference. Although there is variability between the three different clinically distinct subgroups (anisometropic, strabismic and mixed amblyopia), the overall result is clear; the greater the suppression (lower values on the *x*-axes), the greater the amblyopia (larger values on the *y*-axis) ($r^2 = 0.38$, $p < 0.0001$). This relationship is present for each subgroup separately (anisometropic amblyopia, $n = 80$, $r^2 = 0.25$, $p < 0.001$; mixed amblyopia, $n = 9$, $r^2 = 0.39$, $p = 0.07$; strabismic amblyopia, $n = 17$, $r^2 = 0.67$, $p < 0.001$).

In Fig. 3 we see a comparison of three different experimental approaches, each using a different visual stimulus, to further address the relationship between suppression and acuity in amblyopia (Zhou, Huang, & Hess, 2013). Each stimulus is likely to reflect the function of a different cortical area; a local phase discrimination task reflecting mainly V1 function, a global orientation task reflecting ventral extra-striate function and a global motion task (also see Fig. 2) reflecting dorsal extra-striate function. One thing that these different measures have in common is that they all indicate that stronger suppression (though here because of the small *n*, the correlations are not statistically significant) is associated with poorer amblyopic eye acuity.

Measurements of suppression have also been collected in young children using an adaptation of the global motion task previously used in adults (Narasimhan, Harrison, & Giaschi, 2012). These results lend support to a direct relationship between suppression and amblyopia in children. Further support comes from a study of children, teens and adults using a different task where the interocular phase of a low spatial frequency sinusoid was used to measure suppression (Kwon et al., 2014).

Animal studies in which strabismic amblyopia is induced prismatically also argue for a direct relationship between the degree of suppression and the degree of amblyopia in different neuronal populations in visual cortex. The results of Bi et al. (2011) show that stronger suppression is associated with deeper amblyopia in areas V1 and V2 of monkey cortex (Fig. 4).

If suppression was simply a secondary consequence of the monocular loss of function in amblyopia, one would expect weaker suppression to be associated with poorer monocular vision in the amblyopic eye (Holopigian, Blake, & Greenwald, 1988). This is because there would be less information to suppress in patients with deeper amblyopia. The results described above demonstrate the opposite relationship whereby stronger suppression is

associated with a greater loss of monocular vision. This indicates that binocular deficits play a key role in amblyopia and suggests a different approach to therapy, one that tackles the primary binocular problem as a first step.

3.1. A binocular therapeutic approach

A number of laboratory observations led to a way of treating the binocular vision deficit that is associated with amblyopia. First, it was demonstrated that if the interocular contrast was suitably adjusted to compensate for the amblyopic contrast threshold deficit, binocular summation at threshold became normal (Baker et al., 2007). This indicated that strabismic and anisometropic amblyopes were capable of normal binocular function at specially selected interocular contrasts. Second, it was found that normal binocular combination could be achieved at suprathreshold contrasts if the interocular stimulation was suitably balanced between the two eyes (Baker, Meese, & Hess, 2008; Mansouri, Thompson, & Hess, 2008). Thus, even for strabismic adults, if the images of the two eyes are properly aligned and the contrast in the two eyes suitably balanced, information from the two eyes could be combined normally. This demonstrated that humans with amblyopia had latent binocular capabilities and had not been rendered structurally monocular, as previously thought on the basis of the early animal deprivation literature. It was subsequently found that allowing the eyes to combine information under these balanced conditions resulted in a progressive strengthening of binocular fusion and a correspondingly greater tolerance in the interocular contrast differences required to support fusion (i.e. repeated exposure to binocularly balanced stimuli allowed fusion to occur at smaller interocular contrast differences).

This work led to a new dichoptic approach to treatment based on providing viewing conditions that allowed the two eyes to work together and the gradual alteration of interocular contrast differences until binocular combination occurred for all viewing conditions. The treatment, which typically involves 1 h a day for at least 4 days a week over a 4–6 week period, resulted in a re-establishment of binocular vision in the vast majority of cases

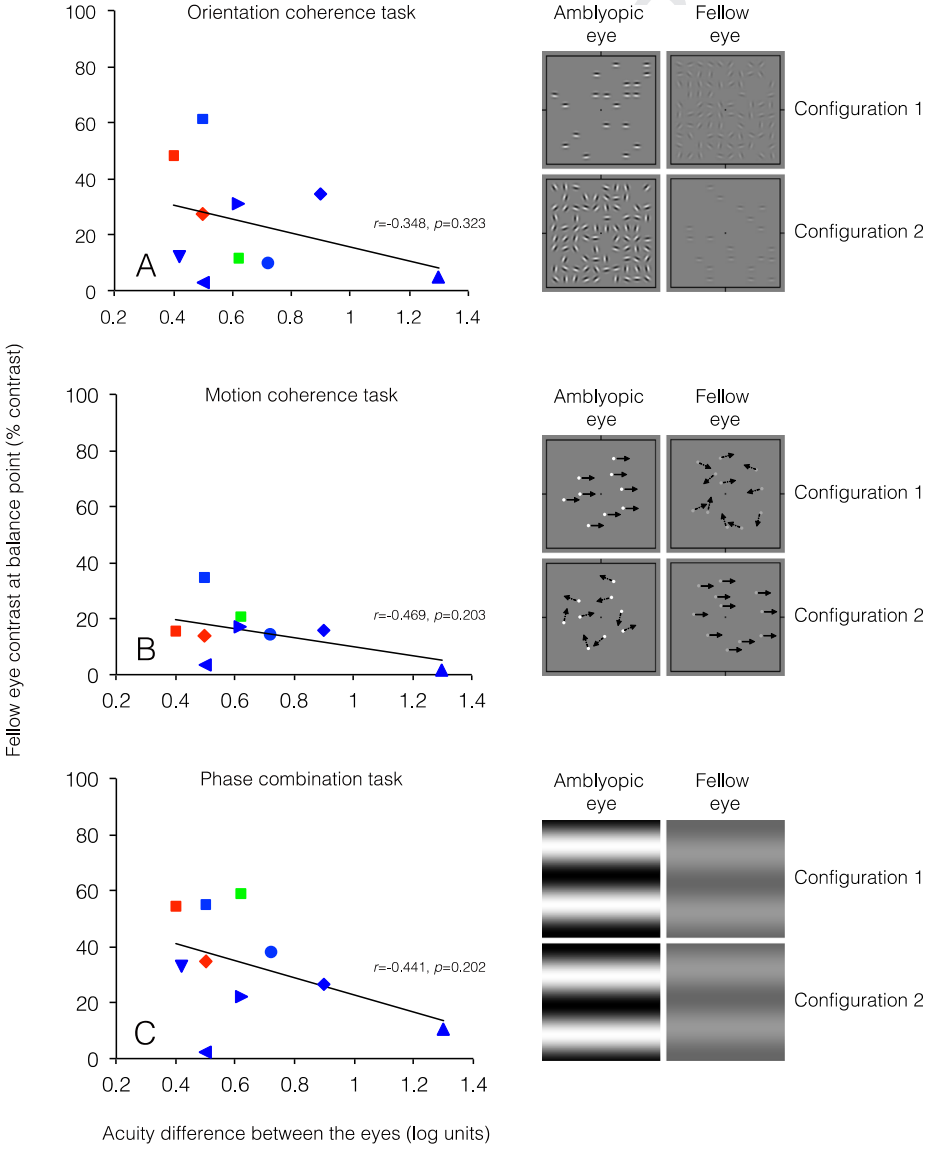

Fig. 3. The relationship between the degree of suppression and acuity difference between the eyes for dichoptic tasks requiring global orientation (top panel), global motion (middle panel) and local phase (bottom panel) judgements. In all panels, different symbols represent different subjects. The solid line represents the best linear fit to the data. On the right of each figure is an illustration of the stimuli used. (Modified from Zhou, Huang, & Hess, 2013).

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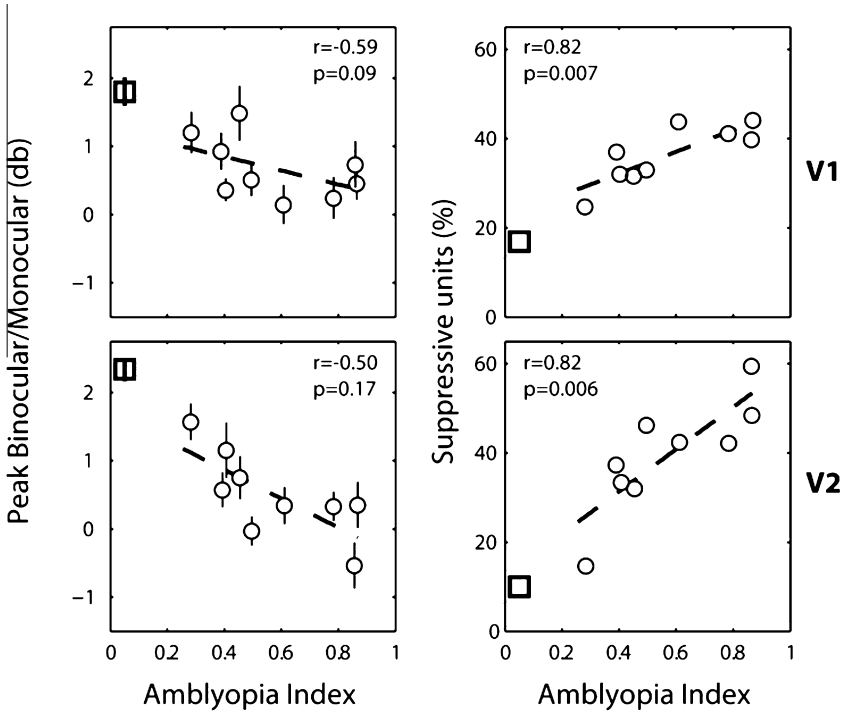

Fig. 4. Relationships between the extent of facilitatory/suppressive binocular interactions (10 log Peak B/M) of V1 (top) and V2 (bottom) neurons in individual strabismic monkeys and the depth of their amblyopia (Amblyopia index values were calculated for each monkey by integrating the area between the contrast sensitivity functions for the operated and fellow eyes and dividing it by the area under the function for the operated eye. This index ranges from 0 (no deficit) to 1.0 (no measurable sensitivity in the operated eye). Relationships are shown between the proportion of binocularly suppressive V1 (i.e., Peak B/M < 0 db) (top) and V2 (bottom) neurons and the depth of amblyopia (AI) (right columns) (from Bi et al., 2011).

regardless of the type of amblyopia or the age of the patient. Furthermore, in the majority of adults, both stereopsis and monocular acuity improved (Hess et al., 2014) though there is not a strong correlation between these two measures. This is not unexpected because the reduction in stereopsis in amblyopia is not solely due to the acuity reduction. To date 192 adults and children have been treated using this approach (Birch et al., 2014; Hess, Mansouri, & Thompson, 2010; Hess et al., 2014; Li, Thompson, et al., 2013; Li et al., 2014; Mansouri et al., 2014; Spiegel, Li, et al., 2013; To et al., 2011) and the results (summarized in Table 1) are promising. For adults (17 years and over), the average improvement in amblyopic eye visual acuity is 0.24 LogMAR ($n = 84$, 95% CI = 0.04 LogMAR, $p < 0.001$). This is shown in Fig. 5A. For compliant children, the average improvement is 0.16 LogMAR ($n = 91$, 95% CI = 0.02, $p < 0.001$). For adults (17 years and over), the average improvement in amblyopic eye stereo is 2.55 log units ($n = 65$, 95% CI – 0.16, $p < 0.001$). This is shown in Fig. 6A. For compliant children, the average stereo improvement is 0.19 log units ($n = 84$, 95% CI = 0.11, $p = 0.001$). This corresponds to an average improvement of 1175 arc s and is shown in Fig. 6B. We have recently shown that the improvements in visual function that result from binocular training cannot be accounted for only by the act of playing a videogame. In particular, binocular training using the falling blocks game results in significantly larger improvements visual acuity and stereopsis than monocular training on the same game (Li, Thompson, et al., 2013).

No adverse effects have been reported from this approach and no patients have reported diplopia because they are always working under conditions where fusion is operating. Over a matter of a few weeks of training, binocular fusion could be extended to all contrasts even when the fixing eye was viewing stimuli at 100% (i.e. natural viewing). To date, this approach has been limited to patients with anisometropic amblyopia or strabismic amblyopia with a small angle of strabismus (<10PD). While it is known that the treatment gains in acuity and stereo are sustained, less is known about the effect of treatment on the motor status of patients with a strabismus. For example, we do not yet know whether these gains in binocular function are the consequence of an ocular re-alignment or in spite of the ocular misalignment.

3.2. Binocular re-balancing; inhibition, attenuation or metaplasticity?

As described above, there is evidence that binocular re-balancing therapy works. However, its neural basis is still a matter of some debate. The most obvious explanation is that reducing the active inhibition of cortical inputs from the amblyopic eye allows for latent binocular function to be realized. Based on what we know about the excitatory and inhibitory circuits involved in binocular combination, the obvious site of this inhibition would be the point at which contralateral inhibitory signals contribute to contrast gain control prior to excitatory binocular combination (Meese, Georgeson, & Baker, 2006; Meese & Hess, 2004). This is shown in schematic form in Fig. 7, which depicts the first stage of a two-stage contrast gain control system. However other explanations include contrast attenuation of the information from the amblyopic eye and synaptic metaplasticity.

3.2.1. Signal inhibition

Support for an active inhibitory process comes mainly from the physiological literature. Mower et al. (1984) showed that the binocularity of over 50% of cortical neurons in strabismic cats could be restored with microiontophoretic injections of bicuculline, a GABA antagonist. Furthermore, primate studies have observed non-specific inhibitory interactions between the eyes of strabismic animals (Sengpiel & Blakemore, 1996; Smith et al., 1997) and Sengpiel et al. (2006) showed that strabismic suppression was

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Table 1
Summary of published studies using dichoptic contrast differences to treat amblyopia. *N* = number of participants, yrs = years, Tx = treatment, aniso = anisometropic amblyopia, strab = strabismic amblyopia, mixed = mixed mechanism amblyopia, tDCS = transcranial direct current stimulation.

	Study	*N*	Age (yrs)	Tx hours	Amblyopia type	Design	Intervention	Display	Acuity improvement (LogMAR)	Stereopsis improvement	Side effects	Compliance	Treatment location	Follow up
Adults	Hess, Mansouri, and Thompson (2010)	9	24–49	5–52	Strab, mixed	Prospective case series	Dichoptic global motion	Stereoscope	0.26 ($p = 0.003$)	8/9 improved ($p = 0.01$)	None	Supervised	Laboratory	N/A
	To et al. (2011)	9	17–51	6–35	Aniso, strab, mixed	Prospective case series	Falling blocks	iPod (lenticular)	0.19 ($p = 0.02$)	5/9 improved ($p = 0.04$)	None	Supervised	Laboratory	N/A
	Li et al. (2013)	18	19–26	10	Aniso, strab, mixed	Patching controlled, crossover	Falling blocks	Video goggles	0.18 ($p < 0.001$)	15/18 improved ($p < 0.001$)	None	Supervised	Laboratory	Stable at 3 months ($n = 5$)
	Spiegel et al. (2013)	16	17–31	11	Aniso, strab, mixed	Sham controlled crossover for tDCS. Dichoptic treatment consistent across groups	Falling blocks + tDCS	iPod (lenticular)	0.34 ($p < 0.001$)	14/16 improved ($p = 0.004$)	None	Supervised	Laboratory	Stable at 3 months ($n = 8$)
Children & adults	Hess et al. (2014)	14	13–50	22–108	Aniso, strab, mixed	Prospective case series	Falling blocks	iPod (lenticular or anaglyphic)	0.11 ($p < 0.001$)	11/14 improved ($p < 0.001$)	Transient asthenopia $N = 1$	On average patients played for 64% of the prescribed treatment time	Home	N/A
	Mansouri et al. (2014)	22	5–73	10–64	Aniso, strab	Prospective case series	Dichoptic global motion	Video goggles	0.34 ($p < 0.001$)	Not measured	None	Supervised	Laboratory	Stable at 6 months ($n = 17$)
Children	Knox et al. (2012)	14	5–14	5	Aniso, strab, mixed	Prospective case series. Participants had plateaued with patching and had stable VA	Falling blocks	Video goggles	0.09 ($p < 0.001$)	7/14 improved ($p = 0.02$)	None	Supervised	School (lunch break)	N/A
	Li et al. (2014)	45	4–12	16–32	Aniso, strab, mixed	Sham controlled	4 dichoptic games including falling blocks	iPad (anaglyphic)	0.08 ($p < 0.001$) compliant only: 0.1 ($p < 0.001$)	5/45 improved ($p > 0.05$) Not significant	None	34/45 played for 4 h or more	Home	Stable at 3 months ($n = 21$)
	Birch et al. (2014)	45	3–7	16–32	Aniso, strab, mixed	Sham controlled	4 dichoptic games including falling blocks	iPad (anaglyphic)	0.09 ($p < 0.001$) compliant only: 0.14 ($p < 0.001$)	3/45 improved ($p = 0.2$) Not significant Compliant children from Li et al. and Birch et al. 12/70 improved, $p = 0.001$	None	28/45 played for 8 h or more	Home	N/A

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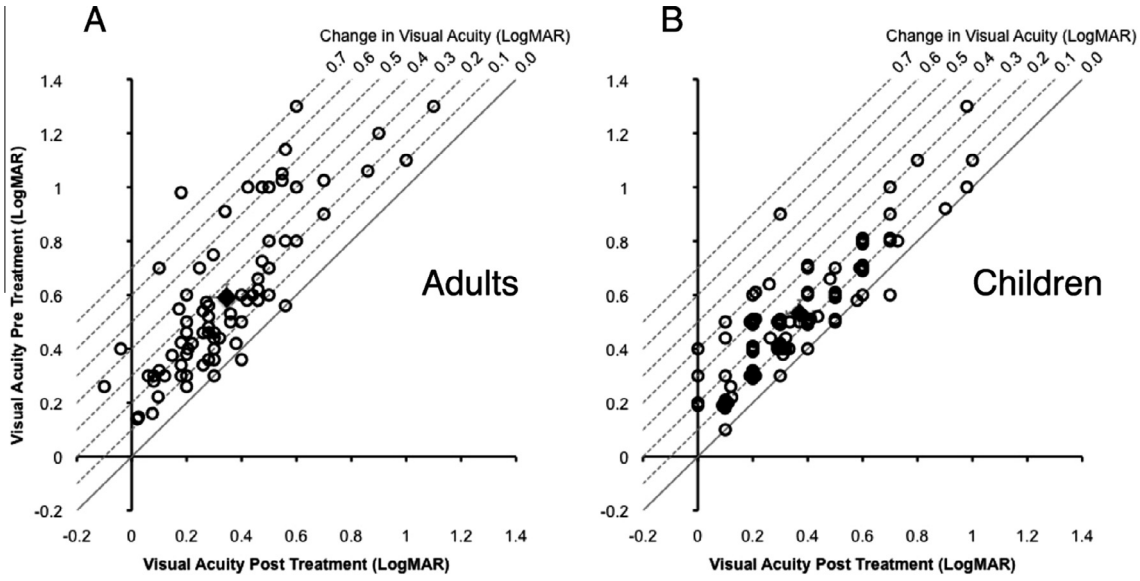

Fig. 5. (A) The combined acuity outcome data from 82 adults with amblyopia across a number of studies (see Table 1). An improvement of 1 line or more on the LogMar chart (0.1 LogMar) is considered significant. The large black triangle (±95% CI) indicates the average improvement. (B) The combined acuity outcome data from 90 children with amblyopia (see Table 1). An improvement of 1 line on the LogMar chart (0.1 LogMar) is considered significant. The large black diamond (±95% CL) indicates the averaged improvement. Only children who complied with treatment are included from the Li et al. (2014) and Birch et al. (2014) papers. Data points are jittered slightly to allow overlapping points to be seen.

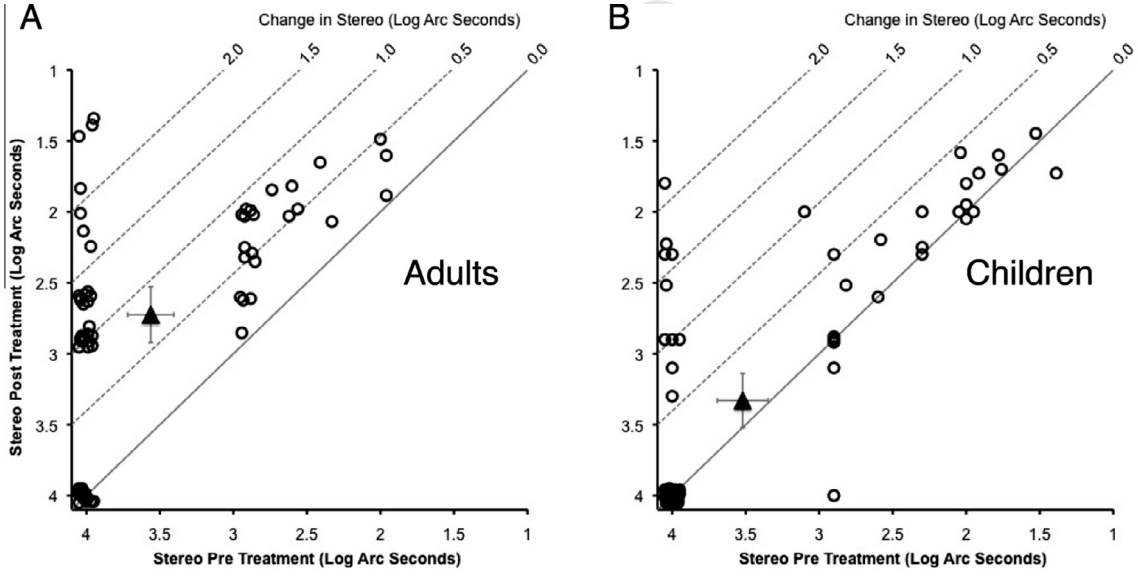

Fig. 6. (A) The combined stereopsis outcome data from 65 adults with amblyopia across a number of studies (see Table 1). Stereopsis was not measured in Mansouri et al. (2014) (n = 17 adults). An improvement of 0.5 log units is considered clinically significant. The large black triangle (±95% CL) indicates the average improvement. (B) The combined stereopsis outcome data from 85 children with amblyopia across a number of studies (see Table 1). Stereopsis was not measured in Mansouri et al. (2014), (n = 5 children). An improvement of 0.5 log units is considered clinically significant. Unmeasurable stereo is assigned a value of 4 log units (10,000 arc s), corresponding to Dmax (Hess, Lui and Wang, 2002). The large black triangle (±95% CL) indicates the mean improvement, which is statistically significant. Only children who complied with treatment are included from the Li et al. (2014) and Birch et al. (2014) papers. Data points are jittered slightly to allow overlapping points to be seen.

mediated by inhibitory interactions involving GABA in the cat (see also Sale & et al., 2007). Recently, Scholl, Tan, and Priebe (2013) showed that in esotropic cats, estimates of the excitatory and inhibitory input to single neurons indicated the presence of binocular suppression occurring as the result of inhibition at the thalamocortical synapse. Modeling suggested that this inhibition was mediated by inhibitory interneurons receiving input from thalamocortical inputs and simple cells, and results in suppression of binocular responses of both simple and complex cells (inherited from their simple cell input). This is illustrated in Fig. 8.

Sengpiel et al. (2006) suggest that the suppression is of a more global nature and possibly involves horizontal connections between same and opposite eye domains in the more superficial layers of the primary visual cortex.

3.2.2. Signal attenuation

Results from human psychophysics relating to the loss of binocular combination in amblyopia have not been as clear cut as the animal neurophysiological data described above (Hess et al., 2014). The studies of Harrad and Hess (1992) provide evidence

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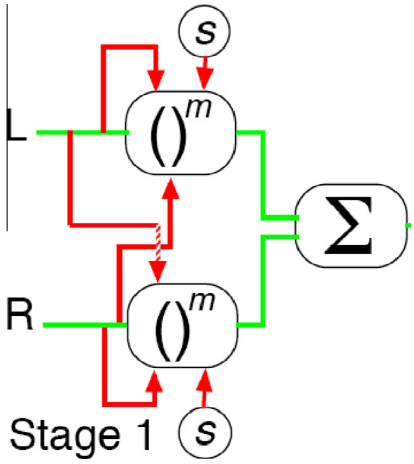

Fig. 7. Excitatory (green) and inhibitory (red) circuits involved in combining information between the two eyes. The inhibitory interocular connections that cross in the center of the schematic model may underpin active suppression. The full circuit involves two stages of contrast gain control each with separate sources of additive noise (S), one before and one after excitatory summation. L = left eye, R = right eye. From Meese and Hess (2004).

for multiple types of "suppression", some involving active inhibition and others not. Fig. 9 illustrates the different forms that suppression can take psychophysically. Here, thresholds are plotted for a dichoptic masking task where the increment to be detected (*y*-axis) is presented to either the amblyopic (filled symbols) or fellow fixing eye (open symbols) and the pedestal that is plotted on the *x*-axis is presented to the other eye. The axes have been normalized to the contrast threshold of each eye, so the monocular contrast deficit for the amblyopic eye has been accounted for. The solid line is the dichoptic masking expected for a normal visual system from the results of Legge and Foley (1980). Results falling on this line indicate normal dichoptic masking. In the results shown in the top left of Fig. 9, a passive monocular attenuation explanation is sufficient and this is true in some observers with anisometropic amblyopia as well as some with strabismic amblyopia (Harrad & Hess, 1992). However, Harrad and Hess' results suggest that there are other forms of interaction that are not amenable to a simple attenuation explanation. In some cases, the strength of the dichoptic influence from the amblyopic to the fixing eye is weaker (top middle panel of Fig. 9) than predicted from the monocular contrast threshold attenuation, in some cases the strength of the dichoptic influence from the fixing to the amblyopic eye is stronger (top right panel of Fig. 9) or weaker (bottom middle panel) than that predicted from the monocular contrast threshold loss. In cases of alternating strabismus, there was simply no interaction between the eyes in either direction (bottom right panel of Fig. 9). Harrad and Hess showed that these suppressive interactions depended on spatial frequency, being much more marked at high spatial frequencies.

There have been a number of subsequent studies of suppression that have provided support for a passive attenuation (or imbalance) rather than for an active inhibition (Baker, Meese, & Hess, 2008; Huang, Baker, & Hess, 2012; Zhou et al., 2014). These results argue that although the dichoptic interactions themselves are normal in amblyopes, the fact that the amblyopic eye needs more contrast to detect stimuli means that stimuli of a fixed suprathreshold contrast will produce less masking from the amblyopic to fellow fixing eye. The resultant interocular imbalance in dichoptic masking will allow the fellow fixing eye to always dominate in binocular viewing. This effect is illustrated in Fig. 10 from the results of Huang et al. (2014) in which one eye views a noise field that is sinusoidally modulated in time and the other eye is briefly presented with letter stimuli of different contrasts at varying time points. Masking is demonstrated by the sinusoidal nature (rectified) of the threshold elevation for detecting the letter stimuli. The results from observers with amblyopia (middle panel) show approximately normal (compared with left panel) masking from fixing to amblyopic eye (dashed curves) but less masking from the amblyopic to fixing eye (solid curves). This is amenable to an explanation based on the reduced contrast sensitivity of the amblyopic eye as demonstrated by the model results (right panel). However, to date this explanation has not been tested directly, a process that would entail using masks that are equi-detectable (at a constant suprathreshold contrast) for each eye. Only then would we know if a simple attenuation explanation could be applied to suppression for this particular paradigm.

As a whole, the psychophysical and physiological explanations for suppression are not in agreement; physiologically there is evidence for active suppression between the two eyes of strabismic animals, psychophysically the picture of suppression is less clear-cut. Simple attenuation of the amblyopic eye together with normal dichoptic inhibitory interactions may both play a part. However, attenuation alone is unlikely to provide a sufficient explanation for the population suppression measures discussed previously.

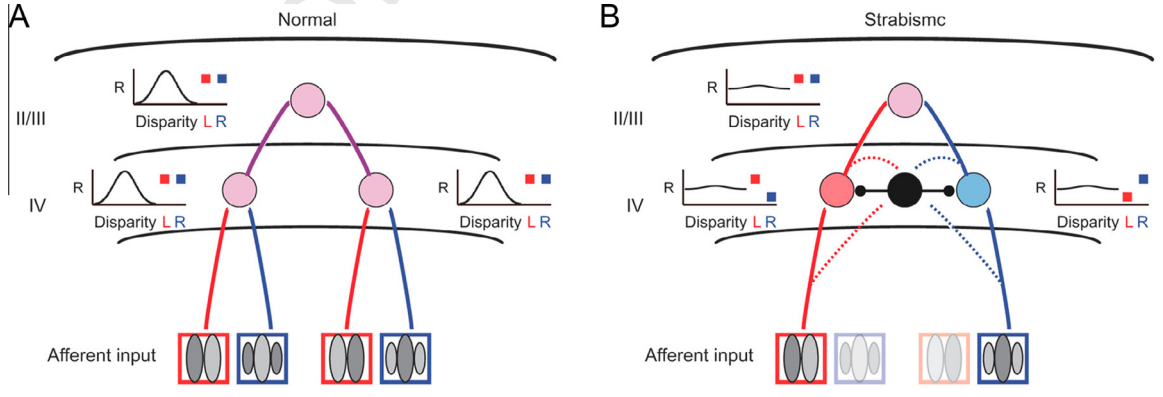

Fig. 8. Loss of thalamic input in a circuit model of strabismus. (A) Left (L) and right (R) eye inputs converge on layer 4 simple cells, generating disparity selectivity. Simple cell inputs converge onto complex cells in layer 2/3, which are also disparity selective. (B) In strabismic animals, simple cells receive monocular input. A loss of binocularity causes a loss of disparity selectivity, which also occurs in complex cells through feedforward inputs. Complex cells receive inputs from simple cells and thus can be binocular. Suppression of binocular responses is mediated by inhibitory interneurons receiving input from thalamocortical inputs and simple cells. In this simple model, the strabismus-induced changes are qualitatively similar for all neurons regardless of the initial difference in synaptic strength, spatial selectivity, and spatial phase between the inputs from each eye to the neuron. (From Scholl, Tan, & Priebe, 2013 – Fig. 9).

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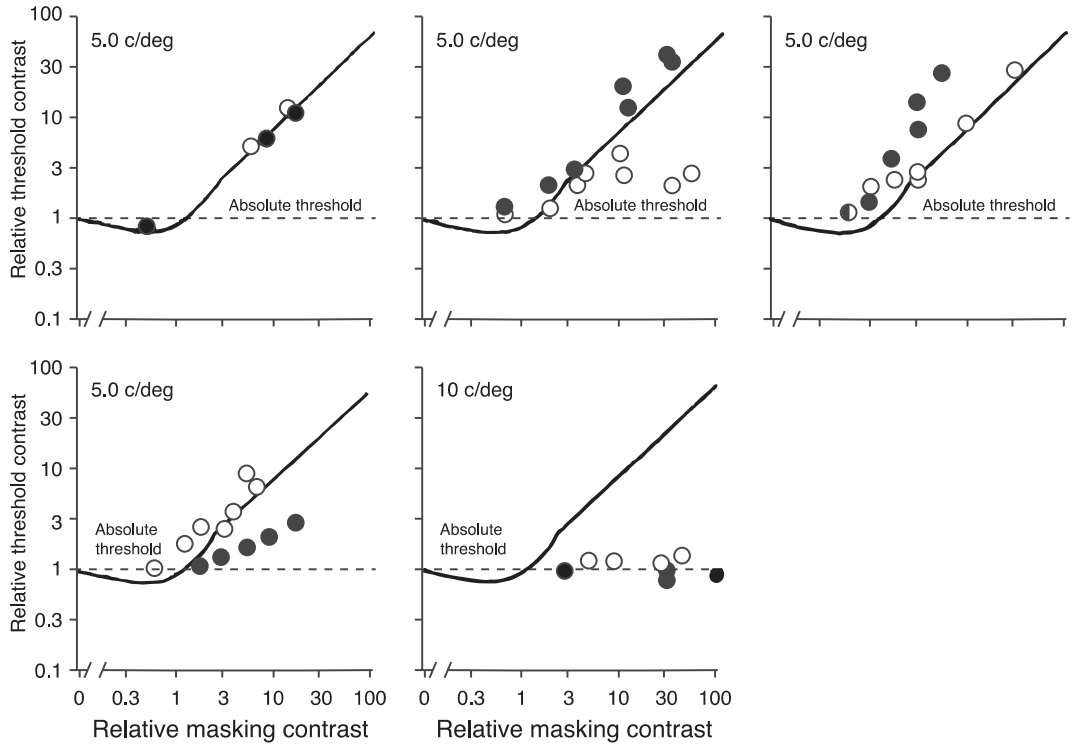

Fig. 9. Dichoptic masking functions for amblyopic observers. The incremental contrast seen by one eye (filled symbols amblyopic eye; open symbols fixing eye) is plotted against the pedestal contrast seen by the other eye. Different categories of response are shown to demonstrate the heterogeneity of suppression in amblyopia, see main text for further information. From Harrad and Hess (1992).

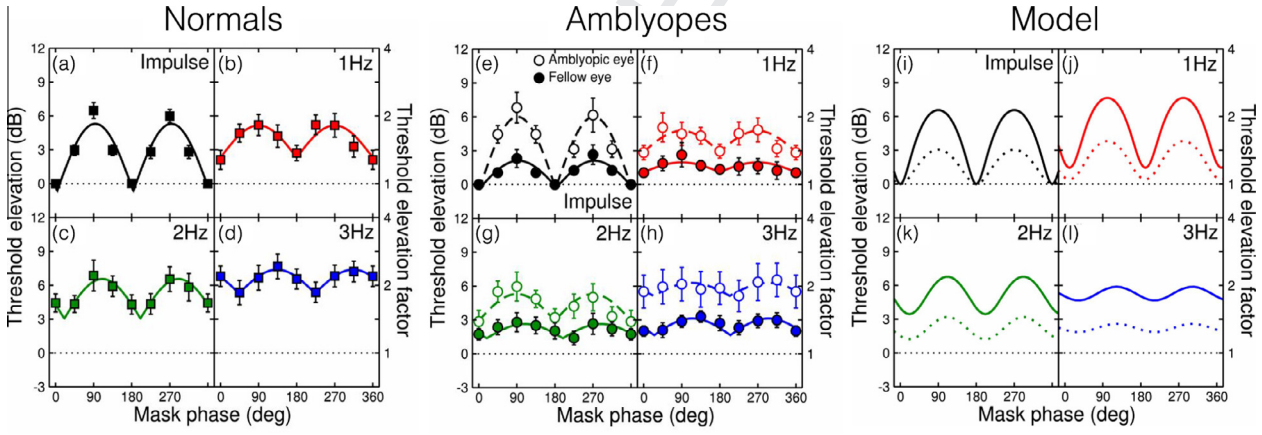

Fig. 10. Dichoptic masking of a briefly presented letter stimulus (open symbols amblyopic eye; filled symbols fellow fixing eye) by the sinusoidal modulation of the contrast of a noise field in the other eye. Results are compared for normals, amblyopes and for a model simulation, see main text for further information. (From Huang et al., 2014).

Monocular contrast sensitivity loss of the amblyopic eye is greatest at high spatial frequencies and minimal or non-existent at very low spatial frequencies (Hess & Howell, 1977; Levi & Harwerth, 1977) and the spatial properties of the global motion and dichoptic phase measures that have been used to date are in the low spatial frequency range. This makes it less likely that monocular attenuation of contrast in the amblyopic eye can account for the results shown in Figs. 2 and 3.

3.2.3. Metaplasticity

Instead of thinking of rebalancing as a means of reducing the interocular inhibition or compensating for signal attenuation, it might be more useful to think about it in terms of synaptic plasticity. Our understanding of plasticity at the level of the synapse has changed considerably over the last decade. An understanding of synaptic plasticity goes well beyond the rules suggested by Hebb whereby synapses "that fire together wire together". Synaptic plasticity is governed by NMDA receptors (Sawtell et al., 2003) which support long-term potentiation (LTP) and long-term depression (LTD) (Cho & Bear, 2010). The way in which this bidirectional synaptic modification operates is itself modifiable. This is termed metaplasticity. Specifically, the threshold change in synaptic input that results in LTP rather than LTD depends on the history of cortical activity as described by the Bienenstock–Cooper–Munro (BCM) theory (Bienenstock, Cooper, & Munro, 1982). Potentiation occurs when activation exceeds this threshold, which itself is a function of the history of neuronal firing. This bidirectional synaptic modification is illustrated in Fig. 11 where the change in

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synaptic strength is plotted against the postsynaptic activity; low levels of post-synaptic activity result in LTD, high levels in LTP. The level of post-synaptic activity corresponding to the transition from LTD to LTP is termed the modification threshold.

Instead of thinking about suppression in terms of an active inhibition or signal attenuation, it could simply be the outcome of synapses with strong fixing eye activation and weak amblyopic eye activation. No matter how strongly the amblyopic eye is activated under these conditions, the synapse will be unable to take advantage of the increased neural activity because its modification threshold is governed by the activity from the fixing eye. However with, for example, dichoptic therapy, when the fixing eye activation is driven down, the modification thresholds may shift in favor of LTP and the weak inputs from the amblyopic eye, that are now more correlated with postsynaptic activity than before, may be able to initiate potentiation via synaptic metaplasticity (see for review, (Cooper & Bear, 2012). The longer the visual system can be kept in a state where the presynaptic activity of both eyes correlates with post synaptic activity, the stronger, more permanent and more balanced will be the ocular dominance. A similar argument has been made concerning the beneficial effects of dark adaptation on ocular dominance plasticity (He et al., 2007). Thought of in these terms, active inhibitory mechanisms or simple signal compensation may not be the right way to conceptualize clinical suppression or the basis of binocular therapy.

3.3. Non-invasive brain stimulation and amblyopia

Non-invasive brain stimulation is another way of modulating excitability and inhibition/suppression within the visual cortex of patients with amblyopia. A number of well established techniques for safely stimulating the human brain are available. These include transcranial magnetic stimulation (TMS), which utilizes magnetic induction to generate weak electrical currents in targeted cortical areas (Barker, Jalinous, & Freeston, 1985; Hallett, 2007) and transcranial direct current stimulation (tDCS) that involves a small (1–2 mA) current passed between two head mounted electrodes (Nitsche & Paulus, 2000). The delivery of repeated pulses of TMS (repetitive TMS; rTMS) can induce lasting increases or decreases in neural excitability depending on the pattern and frequency of stimulation (Fitzgerald, Fountain, & Daskalakis, 2006). tDCS can also induce increases and decreases in excitability depending on the direction of current flow (Nitsche & Paulus, 2000). Anodal tDCS tends to increase excitability where as cathodal tDCS decreases excitability. While the effects of rTMS and tDCS on neural excitability are well documented (Dayan et al., 2013), the underlying mechanisms are yet to be identified. However, a growing number of pharmacological and neurophysiological studies are shedding light on the neural mechanisms involved (Allen et al., 2007; Funke & Benali, 2011; Kozyrev, Eysel, & Jancke, 2014; Stagg & Nitsche, 2011). For example, NMDA receptors appear to be involved in the after-effects of both tDCS and rTMS (Huang et al., 2007; Nitsche et al., 2003), providing a theoretical link to long-term potentiation and long-term depression.

rTMS and tDCS have advanced our understanding of the human brain and have significant potential as tools for rehabilitation. For example, rTMS has been FDA approved for the treatment of depression. Furthermore, the use of rTMS and tDCS to alter pathological patterns of neural excitation and inhibition has shown promise in the treatment of stroke (Hummel & Cohen, 2006; Talelli, Greenwood, & Rothwell, 2007), tinnitus (Vanneste, Langguth, & De Ridder, 2011), chronic pain (Fregni, Freedman, & Pascual-Leone, 2007) and hemispatial neglect (Muri et al., 2013). The use of rTMS to alter abnormal inhibitory interactions between the two cerebral hemispheres in stroke (Hummel & Cohen, 2006) was the inspiration for applying non-invasive brain simulation to amblyopia. As described above, signals from the amblyopic eye evoke low levels of neural activity (Barnes et al., 2001) and may be subject to active inhibition (suppression) within the primary or extrastriate visual cortex (Bi et al., 2011; Sengpiel & Blakemore, 1996). We hypothesized that rTMS would strengthen the response of the visual cortex to inputs from the amblyopic eye (Thompson et al., 2012). This idea was based on reports that rTMS could reduce intracortical inhibition (Fitzgerald, Fountain, & Daskalakis, 2006), at least within the motor cortex, and therefore may reduce inhibition of information from the amblyopic eye. Furthermore, rTMS had been shown to have a homeostatic effect, with inhibited neural populations being more susceptible to excitatory stimulation and populations with high levels of excitation being more susceptible to inhibitory stimulation (Silvanto, Muggleton, & Walsh, 2008). Therefore, excitatory rTMS protocols may preferentially affect inputs from the amblyopic eye whereas inhibitory protocols may target fellow eye inputs. In this scenario, the net effect of either an excitatory or inhibitory rTMS protocol would be a reduction in the activation difference between cortical inputs from the two eyes.

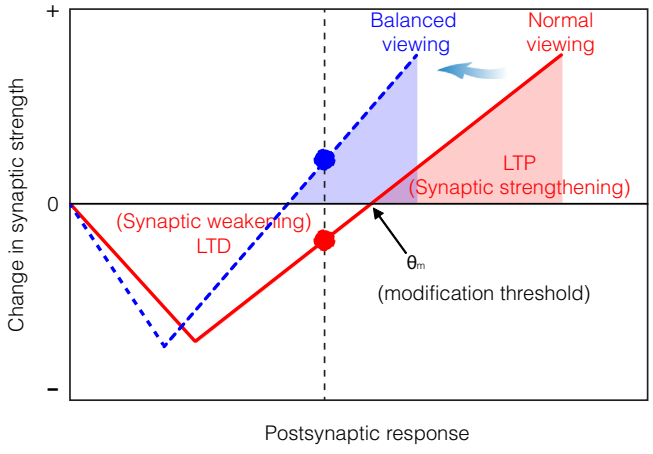

Fig. 11. The BCM theory of synaptic plasticity includes a sliding modification threshold that depends on the history of postsynaptic activity. The value of the modification threshold is shown for two conditions; normal viewing where the activity of the fixing eye dominates and a balanced viewing condition where the activity of the fixing eye has been reduced so that the amblyopic eye activity which was previously depressed (LTD) is now potentiated (LTP). Adapted from Cooper and Bear (2012).

Our first study in a small group of adults with amblyopia supported this hypothesis; both excitatory and inhibitory rTMS protocols increased amblyopic eye contrast sensitivity by an average of 40%, with excitatory rTMS having a more consistent effect across participants (Thompson et al., 2008). Stimulation of the motor cortex had no effect. As part of the procedure for the calibration of stimulus intensity, we measured phosphene thresholds in both patients and controls. Phosphene thresholds are the lowest intensity of single pulse of visual cortex TMS that can elicit the percept of a phosphene and are often used as a measure of visual cortex excitability (Antal et al., 2003; Aurora, Welch, & Al-Sayed, 2003). Unexpectedly, we found that patients with amblyopia had significantly higher phosphene thresholds than controls (Fig. 12A). This preliminary finding suggests that the visual cortex of patients with amblyopia has lower overall levels of excitability that controls, possibly due to suppressive interactions.

In our original study, the effects of rTMS on contrast sensitivity were transient, returning to baseline within 24 h in most cases. In a follow up study, we found that repeated administration of visual cortex continuous theta burst stimulation (cTBS, a form of rTMS that requires only a short stimulation period) over 5 days led to

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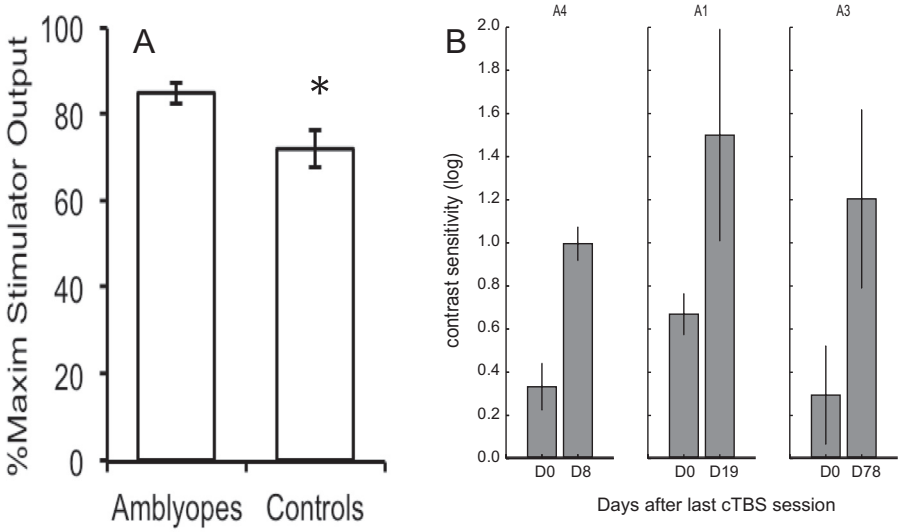

Fig. 12. Transcranial magnetic stimulation and amblyopia. Panel A shows phosphene thresholds for patients with amblyopia ($n = 9$) and controls ($n = 5$). Larger values on the y-axis indicate that greater intensities of single pulse TMS were required to elicit the perception of a phosphene. Patients with amblyopia had significantly higher phosphene thresholds than controls ($t_{12} = 2.8$, $p = 0.02$) suggesting lower levels of visual cortex excitability. Data from Thompson et al. (2008). Panel B shows contrast sensitivity data from three patients treated with 5 daily sessions of visual cortex continuous theta burst stimulation (cTBS). cTBS induced improvements in amblyopic eye contrast sensitivity that lasted up to 78 days (D0 = baseline). Figure from Clavagnier, Thompson, and Hess (2013).

long lasting improvements in contrast sensitivity that were stable over a period of up to 78 days (Clavagnier, Thompson, & Hess, 2013) (Fig. 12B). This indicates that multiple doses of cTBS may lead to lasting and perhaps permanent improvements in visual function in adults with amblyopia. Only three to four repeated (one per day) applications of cTBS were required to produce long-term, stable improvements.

In a parallel series of studies, we have investigated the effect of tDCS on amblyopic eye contrast sensitivity (Spiegel, byblow, et al., 2013). This work was motivated by a magnetic resonance spectroscopy study, which revealed that anodal tDCS acted to reduce the concentration of GABA when applied to the motor cortex (Stagg et al., 2009). We hypothesized that anodal tDCS would have a similar effect on the visual cortex and may, therefore, reduce suppression and improve vision in patients with amblyopia. Before applying tDCS to patients with amblyopia, we first investigated the effects of anodal tDCS on psychophysically measured surround suppression in observers with normal vision (Spiegel et al., 2012). Surround suppression is thought to involve GABA-mediated inhibitory interactions within the primary visual cortex (Yoon et al., 2010). Anodal tDCS significantly attenuated surround suppression, but had no effect on overlay suppression, a control condition that does not involve inhibition in V1. Cathodal tDCS had no effect on either condition. Based on these results, anodal tDCS was applied to the visual cortex of thirteen patients with amblyopia. Eight out of thirteen patients experienced transient improvements in contrast sensitivity in response to anodal but not cathodal tDCS (Spiegel, Byblow, et al., 2013). There were no obvious clinical or demographic differences between the group of patients who showed improvements and those that did not, however individual differences in the response to tDCS are well documented and have been linked to a range of variables including patterns of functional connectivity within neural networks (Vanneste et al., 2011). To ensure that the effects we observed were due to tDCS-induced changes within the visual cortex, we used fMRI to measure the relative response of V1, V2 and V3 to contrast reversing checkerboards shown to the amblyopic vs. the fellow eyes. After sham tDCS, large areas of the primary and extrastriate visual cortex showed a significantly larger response to the fellow eye than the amblyopic eye in agreement with previous studies demonstrating that the amblyopic eye is less able to activate the visual cortex (Barnes et al., 2001). This bias towards stronger activation in the fellow eye was reduced by anodal tDCS, with significant effects observed in V2 and V3. Anodal tDCS may have normalized the cortical response to information from each eye, possibly by reducing suppression within the visual cortex.

The finding the anodal tDCS may act to reduce suppression in the visual cortex raised the possibility that anodal tDCS could also enhance the effects of dichoptic treatment. In a recent study we demonstrated that this was indeed the case, anodal tDCS combined with dichoptic treatment led to significantly greater improvements in stereopsis than sham tDCS combined with dichoptic treatment (Spiegel, Li, et al., 2013). This effect was not present for monocular measures of effects of anodal tDCS were limited to binocular visual function.

Non-invasive brain stimulation is now an established technique in many fields, however research into the use of brain stimulation to promote recovery of vision is sill in its infancy. Furthermore, as described above, mechanistic studies of noninvasive brain stimulation have mostly focused to the motor cortex and it is not clear how these findings translate to the visual cortex. The initial results summarized here indicate that non-invasive brain stimulation is a useful tool for investigating and potentially treating the neural basis of amblyopia. Future work will establish whether non-invasive brain stimulation has a role in amblyopia treatment, either as a stand-alone therapy or in combination with other interventions such as binocular therapy.

When considered in the context of inhibition, attenuation and metaplasticity, the effects of rTMS and tDCS on amblyopic eye function are consistent with reductions in inhibition or attenuation of information from the amblyopic eye, which may be permissive for synaptic plasticity. On the basis of current data it is not possible to definitively distinguish between changes in inhibition and attenuation. However, the preliminary data indicating abnormally

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high levels of inhibition within the amblyopic visual cortex (Fig. 10A), combined with the ability of anodal tDCS to reduce surround suppression and GABA concentration favor a reduction in inhibition/suppression.

4. Conclusions

Suppression is an important part of the amblyopia syndrome and the positive correlation between suppression and the depth of amblyopia indicates that binocular dysfunction is the primary problem. Numerous studies demonstrating that balancing the information seen by the two eyes can promote binocular function and lead to a re-establishment of binocular vision further support this idea. These advances have raised a number of questions that are yet to be answered: Is the basis for the original imbalance between the amblyopic and fellow eyes signal attenuation, signal inhibition, metaplasticity or a combination of these? Do binocular therapy and non-invasive brain stimulation lead to reduced active cortical inhibition, a change in synaptic metaplasticity or the two in concert? Answers to these questions will provide new insights into amblyopia and the mechanisms controlling plasticity within the adult human visual cortex.

5. Uncited reference

Goodman et al. (2011).

Acknowledgments

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References

Allen, E. A., Pasley, B. N., Duong, T., & Freeman, R. D. (2007). Transcranial magnetic stimulation elicits coupled neural and hemodynamic consequences. *Science, 317*(5846), 1918–1921.

Antal, A., Kincses, T. Z., Nitsche, M. A., & Paulus, W. (2003). Manipulation of phosphene thresholds by transcranial direct current stimulation in man. *Experimental Brain Research, 150*(3), 375–378.

Aurora, S., Welch, K., & Al-Sayed, F. (2003). The threshold for phosphenes is lower in migraine. *Cephalalgia, 23*(4), 258–263.

Baker, D. H., Meese, T. S., & Hess, R. F. (2008). Contrast masking in strabismic amblyopia: Attenuation, noise, interocular suppression and binocular summation. *Vision Research, 48*(15), 1625–1640.

Baker, D. H., Meese, T. S., Mansouri, B., & Hess, R. F. (2007). Binocular summation of contrast remains intact in strabismic amblyopia. *Investigative Ophthalmology & Visual Science, 48*(11), 5332–5338.

Barker, A. T., Jalinous, R., & Freeston, I. L. (1985). Non-invasive magnetic stimulation of human motor cortex. *Lancet, 1*(8437), 1106–1107.

Barnes, G. R., Hess, R. F., Dumoulin, S. O., Achtman, R. L., & Pike, G. B. (2001). The cortical deficit in humans with strabismic amblyopia. *Journal of Physiology, 533*(Pt 1), 281–297.

Bi, H., Zhang, B., Tao, X., Harwerth, R. S., Smith, E. L., III, & Chino, Y. M. (2011). Neuronal responses in visual area V2 (V2) of macaque monkeys with strabismic amblyopia. *Cerebral Cortex* (in press).

Bienenstock, E. L., Cooper, L. N., & Munro, P. W. (1982). Theory for the development of neuron selectivity: Orientation specificity and binocular interaction in visual cortex. *Journal of Neuroscience, 2*, 32–48.

Birch, E. E., Li, S., Jost, R. M., Subramanian, V., Morale, S. E., Stager, D. Jr.,, et al. (2014). Binocular iPad treatment for amblyopia in preschool children. *Journal of American Association for Pediatric Ophthalmology and Strabismus (JAAPOS), 18*(4), e1–e2.

Bonneh, Y. S., Sagi, D., & Polat, U. (2004). Local and non-local deficits in amblyopia: Acuity and spatial interactions. *Vision Research, 44*, 3099–3110.

Campbell, F. W., Hess, R. F., Watson, P. G., & Banks, R. (1978). Preliminary results of a physiologically based treatment of amblyopia. *British Journal of Ophthalmology, 62*(11), 748–755.

Cho, K. K., & Bear, M. F. (2010). Promoting neurological recovery of function via metaplasticity. *Future Neurology, 5*(1), 21–26.

Clavagnier, S., Thompson, B., & Hess, R. F. (2013). Long lasting effects of daily theta Burst rTMS sessions in the human amblyopic cortex. *Brain Stimulation*.

Cleary, M., Moody, A. D., Buchanan, A., Stewart, H., & Dutton, G. N. (2009). Assessment of a computer-based treatment for older amblyopes: The Glasgow Pilot Study. *Eye, 23*(1), 124–131.

Cooper, L. N., & Bear, M. F. (2012). The BCM theory of synapse modification at 30: Interaction of theory with experiment. *Nature Reviews Neuroscience, 13*(11), 798–810.

Dayan, E., Censor, N., Buch, E. R., Sandrini, M., & Cohen, L. G. (2013). Noninvasive brain stimulation: From physiology to network dynamics and back. *Nature Neuroscience, 16*(7), 838–844.

Fitzgerald, P. B., Fountain, S., & Daskalakis, Z. J. (2006). A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology, 117*(12), 2584–2596.

Fregni, F., Freedman, S., & Pascual-Leone, A. (2007). Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. *Lancet Neurology, 6*(2), 188–191.

Funke, K., & Benali, A. (2011). Modulation of cortical inhibition by rTMS – Findings obtained from animal models. *Journal of Physiology, 589*(Pt 18), 4423–4435.

Goodman, L., Black, J. M., Phillips, G., Hess, R. F., & Thompson, B. (2011). Excitatory binocular interactions in two cases of alternating strabismus. *Journal of the American Association of pediatric Ophthalmology and Strabismus* (in press).

Hallett, M. (2007). Transcranial magnetic stimulation: A primer. *Neuron, 55*(2), 187–199.

Harrad, R. A., & Hess, R. F. (1992). Binocular integration of contrast information in amblyopia. *Vision Research, 32*, 2135–2150.

He, H. Y., Ray, B., Dennis, K., & Quinlan, E. M. (2007). Experience-dependent recovery of vision following chronic deprivation amblyopia. *Nature Neuroscience, 10*, 1134–1136.

Hess, R. F., Babu, R. J., Clavagnier, S., Black, J., Bobier, W., & Thompson, B. (2014). The IPOD binocular home-based treatment for amblyopia in adults: Efficacy and compliance. *Experimental and Clinical Optometry* (in press).

Hess, R. F., & Howell, E. R. (1977). The threshold contrast sensitivity function in strabismic amblyopia: Evidence for a two type classification. *Vision Research, 17*(9), 1049–1055.

Hess, R. F., Mansouri, B., & Thompson, B. (2010). A new binocular approach to the treatment of amblyopia in adults well beyond the critical period of visual development. *Restorative Neurology and Neuroscience, 28*, 1–10.

Hess, R. F., Thompson, B., & Baker, D. H. (2014). Binocular vision in amblyopia: Structure, suppression and plasticity. *Ophthalmic and Physiological Optics, 34*(2), 146–162.

Holmes, J. M., Beck, R. W., Kraker, R. T., Astle, W. F., Birch, E. E., Cole, S. R., et al. (2004). Risk of amblyopia recurrence after cessation of treatment. *Journal of American Association for Pediatric Ophthalmology and Strabismus (JAAPOS), 8*(5), 420–428.

Holmes, J. M., Beck, R. W., Kraker, R. T., Cole, S. R., Repka, M. X., Birch, E. E., et al. (2003). Impact of patching and atropine treatment on the child and family in the amblyopia treatment study. *Archives of Ophthalmology, 121*(11), 1625–1632.

Holopigian, K., Blake, R., & Greenwald, M. J. (1988). Clinical suppression and amblyopia. *Investigative Ophthalmology & Visual Science, 29*(3), 444–451.

Huang, P. C., Baker, D. H., & Hess, R. F. (2012). Interocular suppression in normal and amblyopic vision: Spatio-temporal properties. *Journal of Vision, 12*(11).

Huang, Y. Z., Chen, R. S., Rothwell, J. C., & Wen, H. Y. (2007). The after-effect of human theta burst stimulation is NMDA receptor dependent. *Clinical Neurophysiology, 118*(5), 1028–1032.

Hummel, F. C., & Cohen, L. G. (2006). Non-invasive brain stimulation: A new strategy to improve neurorehabilitation after stroke? *Lancet Neurology, 5*(8), 708–712.

Kozyrev, V., Eysel, U. T., & Jancke, D. (2014). Voltage-sensitive dye imaging of transcranial magnetic stimulation-induced intracortical dynamics. *Proceedings of the National academy of Sciences of the United States of America, 111*(37), 13553–13558.

Kwon, M., Lu, Z. L., Miller, A., Kazlas, M., Hunter, D. G., & Bex, P. J. (2014). Assessing binocular interaction in amblyopia and its clinical feasibility. *PLoS One, 9*(6), e100156.

Legge, G. E., & Foley, J. M. (1980). Contrast masking in human vision. *Journal of the Optical Society of America, 70*, 1458–1471.

Levi, M., & Harwerth, R. S. (1977). Spatio-temporal interactions in anisometropic and strabismic amblyopia. *Investigative Ophthalmology & Visual Science, 16*(1), 90–95.

Li, J., Hess, R. F., Chan, L. Y., Deng, D., Yang, X., Chen, X., et al. (2013). Quantitative measurement of interocular suppression in anisometropic amblyopia: A case-control study. *Ophthalmology, 120*(8), 1672–1680.

Li, S. L., Jost, R. M., Morale, S. E., Stager, D. R., Dao, L., Stager, D., et al. (2014). A binocular iPad treatment for amblyopic children. *Eye, 28*(10), 1246–1253.

Li, J., Thompson, B., Deng, D., Chan, L. Y., Yu, M., & Hess, R. F. (2013). Dichoptic training enables the adult amblyopic brain to learn. *Current Biology, 23*(8), R308–309.

Li, J., Thompson, B., Lam, C. S. Y., Deng, D., Chan, L. Y. L., Maehara, G., et al. (2011). The role of suppression in amblyopia. *Investigative Ophthalmology & Visual Science, 52*(7), 4167–4176.

Li, R. W., Young, K. G., Hoenig, P., & Levi, D. M. (2005). Perceptual learning improves visual performance in juvenile amblyopia. *Investigative Ophthalmology & Visual Science, 46*, 3161–3168.

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Mansouri, B., Singh, P., Globa, A., & Pearson, P. (2014). Binocular training reduces amblyopic visual acuity impairment. *Strabismus, 22*(1), 1–6.

Mansouri, B., Thompson, B., & Hess, R. F. (2008). Measurement of suprathreshold binocular interactions in amblyopia. *Vision Research, 48*(28), 2775–2784.

McKee, S. P., Levi, D. M., & Movshon, J. A. (2003). The pattern of visual loss in amblyopia. *Journal of Vision, 3*(5), 380–405.

Meese, T. S., Georgeson, M. A., & Baker, D. H. (2006). Binocular contrast vision at and above threshold. *Journal of Vision, 6*(11), 1224–1243.

Meese, T. S., & Hess, R. F. (2004). Low spatial frequencies are suppressively masked across spatial scale, orientation, field position, and eye of origin. *Journal of Vision, 4*(10), 843–859.

Mitchell, D. E., Howell, E. R., & Keith, C. G. (1983). The effect of minimal occlusion therapy on binocular visual functions in amblyopia. *Investigative Ophthalmology & Visual Science, 24*(6), 778–781.

Mower, G. D., Christen, W. G., Burchfiel, J. L., & Duffy, F. H. (1984). Microiontophoretic bicuculline restores binocular responses to visual cortical neurons in strabismic cats. *Brain Research, 309*(1), 168–172.

Muri, R. M., Cazzoli, D., Nef, T., Mosimann, U. P., Hopfner, S., & Nyffeler, T. (2013). Non-invasive brain stimulation in neglect rehabilitation: An update. *Frontier in Human Neuroscience, 7*, 248.

Narasimhan, S., Harrison, E. R., & Giaschi, D. E. (2012). Quantitative measurement of interocular suppression in children with amblyopia. *Vision Research, 66*, 1–10.

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., et al. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *Journal of Physiology, 553*(Pt 1), 293–301.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology, 527*(Pt 3), 633–639.

Noah, S., Bayliss, J., Vedamurthy, I., Nahum, M., Levi, D. M., & Bavelier, D. (2014). Comparing dichoptic action video game play to patching in adults with amblyopia. *IOVS, 173*. May 16–21.

Ooiemail, T. L., Su, Y. R., Natale, D. M., & He, Z. J. (2013). A push–pull treatment for strengthening the 'lazy eye' in amblyopia. *Current Biology, 23*(8), R309–R310.

Polat, U., Bonneh, Y., Ma-Naim, T., Belkin, M., & Sagi, D. (2005). Spatial interactions in amblyopia: Effects of stimulus parameters and amblyopia type. *Vision Research, 45*, 1471–1479.

Polat, U., Ma-Naim, T., Belkin, M., & Sagi, D. (2004). Improving vision in adult amblyopia by perceptual learning. *Proceedings of the National academy of Sciences of the United States of America, 101*(17), 6692–6697.

Press, L. J. (1981). Electronic games and strabismic therapy. *Journal of Optomery and Visual Development, 12*(3), 35–39.

Sale, A. et al. (2007). Environmental enrichment in adulthood promotes amblyopia recovery through a reduction of intracortical inhibition. *Nature Neuroscience, 10*, 679–681.

Sawtell, N. B., Frenkel, M. Y., Philpot, B. D., Nakazawa, K., Tonegawa, S., & Bear, M. F. (2003). NMDA receptor-dependent ocular dominance plasticity in adult visual cortex. *Neuron, 38*, 977–985.

Scholl, B., Tan, Y. Y. A., & Priebe, N. J. (2013). Strabismus disrupts synaptic integration in primary visual cortex. *The Journal of Neuroscience, 33*(34), 17108–17122.

Sengpiel, F., & Blakemore, C. (1996). The neural basis of suppression and amblyopia in strabismus. *Eye, 10*(Pt 2), 250–258.

Sengpiel, F., Jirmann, K.-U., Vorobyov, V., & Eysel, U. (2006). Strabismic suppression is mediated by interactions in the primary visual cortex. *Cerebral Cortex, 16*, 1750–1758.

Silvanto, J., Muggleton, N., & Walsh, V. (2008). State-dependency in brain stimulation studies of perception and cognition. *Trends in Cognitive Science, 12*(12), 447–454.

Smith, E. L., 3rd, Chino, Y. M., Ni, J., Cheng, H., Crawford, M. L., & Harwerth, R. S. (1997). Residual binocular interactions in the striate cortex of monkeys reared with abnormal binocular vision. *Journal of Neurophysiology, 78*(3), 1353–1362.

Spiegel, D. P., Byblow, W. D., Hess, R. F., & Thompson, B. (2013). Anodal Transcranial direct current stimulation transiently improves contrast sensitivity and normalizes visual cortex activation in individuals with amblyopia. *Neurorehabilitation and Neural Repair*.

Spiegel, D. P., Hansen, B. C., Byblow, W. D., & Thompson, B. (2012). Anodal transcranial direct current stimulation reduces psychophysically measured surround suppression in the human visual cortex. *PLoS One, 7*(5), e36220.

Spiegel, D. P., Li, J., Hess, R. F., Byblow, W. D., Deng, D., Yu, M., et al. (2013). Transcranial direct current stimulation enhances recovery of stereopsis in adults with amblyopia. *Neurotherapeutics, 10*(4), 831–839.

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., et al. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *Journal of Neuroscience, 29*(16), 5202–5206.

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *Neuroscientist, 17*(1), 37–53.

Talelli, P., Greenwood, R. J., & Rothwell, J. C. (2007). Exploring theta burst stimulation as an intervention to improve motor recovery in chronic stroke. *Clinical Neurophysiology, 118*(2), 333–342.

Thompson, B., Mansouri, B., Koski, L., & Hess, R. F. (2008). Brain plasticity in the adult: Modulation of function in amblyopia with rTMS. *Current Biology, 18*(14), 1067–1071.

Thompson, B., Mansouri, B., Koski, L., & Hess, R. F. (2012). From motor cortex to visual cortex: The application of noninvasive brain stimulation to amblyopia. *Developmental Psychobiology, 54*(3), 263–273.

To, L., Thompson, B., Blum, J., Maehara, G., Hess, R. F., & Cooperstock, J. (2011). A game platform for treatment of amblyopia. *IEEE Transactions on Neural Systems & Rehabilitation Engineering, 19*(30), 280–289.

Vanneste, S., Focquaert, F., Van de Heyning, P., & De Ridder, D. (2011). Different resting state brain activity and functional connectivity in patients who respond and not respond to bifrontal tDCS for tinnitus suppression. *Experimental Brain Research, 210*(2), 217–227.

Vanneste, S., Langguth, B., & De Ridder, D. (2011). Do tDCS and TMS influence tinnitus transiently via a direct cortical and indirect somatosensory modulating effect? A combined TMS-tDCS and TENS study. *Brain Stimulation, 4*(4), 242–252.

Webber, A. L., Wood, J. M., Gole, G. A., & Brown, B. (2008). Effect of amblyopia on self-esteem in children. *Optometry and Vision Science, 85*(11), 1074–1081.

Yoon, J. H., Maddock, R. J., Rokem, A., Silver, M. A., Minzenberg, M. J., Ragland, J. D., et al. (2010). GABA concentration is reduced in visual cortex in schizophrenia and correlates with orientation-specific surround suppression. *Journal of Neuroscience, 30*(10), 3777–3781.

Zhou, J., Huang, P. C., & Hess, R. F. (2013). Interocular suppression in amblyopia for global orientation processing. *Journal of Vision, 13*(5), 19.

Zhou, J., McNeal, S., Babu, R. J., Baker, D., Bobier, W., & Hess, R. F. (2014). Time course of dichoptic masking in normals and suppression in amblyopes. *Investigative Ophthalmology & Visual Science, 55*(7), 4098–4104.

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