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.

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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
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

![Amblyopia therapies diagram]

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” (Ooiemait 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 4 dot test in which stimuli of different colors are presented anaesthetically 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 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) (r² = 0.38, p < 0.0001). This relationship is present for each subgroup separately (anisometropic amblyopia, n = 80, r² = 0.25, p < 0.001; mixed amblyopia, n = 9, r² = 0.39, p = 0.07; strabismic amblyopia, n = 17, r² = 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, & Giacchi, 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 pragmatically 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.

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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).
No adverse effects have been reported from this approach and 289 patients with anisometropic amblyopia or strabismic amblyopia 288 (i.e., natural viewing). To date, this approach has been limited to 287 contrasts even when the fixing eye was viewing stimuli at 100% 286 few weeks of training, binocular fusion could be extended to all 285 ing under conditions where fusion is operating. Over a matter of a 284 no patients have reported diplopia because they are always work- 283 ing on the same game (Li, Thompson, et al., 2013).  

Improvements visual acuity and stereopsis than monocular train- 279 the act of playing a videogame. In particular, binocular training 278 that result from binocular training cannot be accounted for only by 277 We have recently shown that the improvements in visual function 276 to an average improvement of 1.175 arc s and is shown in Fig. 6B. 275 is 0.19 log units (Fig. 6A. For compliant children, the average improvement is 0.16 273 2.55 log units (Fig. 5A. For compliant children, the average improvement is 0.16 270 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. 258 Furthermore, in the majority of adults, both stereopsis and monoc- 257 uar acuity improved (Hess et al., 2014) though there is not a strong 256 correlation between these two measures. This is not unexpected 255 because the reduction in stereopsis in amblyopia is not solely 254 due to the acuity reduction. To date 192 adults and children have 253 been treated using this approach (Birch et al., 2014; Hess, 254 Mansouri, & Thompson, 2010; Hess et al., 2014; Li, Thompson, 255 et al., 2013; Li et al., 2014; Mansouri et al., 2014; Spiegel, Li, 256 et al., 2013; To et al., 2011) and the results (summarized in 257 Table 1) are promising. For adults (17 years and over), the average 256 improvement in amblyopic eye visual acuity is 0.24 LogMAR 255 (n = 84, 95% CI = 0.04 LogMAR, p < 0.001). This is shown in 252 Fig. 5A. For compliant children, the average improvement is 0.16 251 LogMAR (n = 91, 95% CI = 0.02, p < 0.001). For adults (17 years 250 and over), the average improvement in amblyopic eye stereovis- 249 ual contrast is 2.55 log units (n = 65, 95% CI = 0.16, p < 0.001). This is shown in 246 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 1.75 arc s and is shown in Fig. 6B. 243 We have recently shown that the improvements in visual function that result from binocular training cannot be accounted for only by 242 the act of playing a videogame. In particular, binocular training 241 using the falling blocks game results in significantly larger 240 improvements visual acuity and stereopsis than monocular train- 239 ing on the same game (Li, Thompson, et al., 2013). 240 No adverse effects have been reported from this approach and 239 no patients have reported diplopia because they are always work- 238 ing under conditions where fusion is operating. Over a matter of a 237 few weeks of training, binocular fusion could be extended to all 236 contrasts even when the fixing eye was viewing stimuli at 100% 235 (i.e., natural viewing). To date, this approach has been limited to 234 patients with anisometropic amblyopia or strabismic amblyopia 233 with a small angle of strabismus (<10PD). While it is known that 232 the treatment gains in acuity and stereo are sustained, less is 231 known about the effect of treatment on the motor status of 230 patients with a strabismus. For example, we do not yet know 229 whether these gains in binocular function are the consequence of 228 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-balanc- 297 ing therapy works. However, its neural basis is still a matter of 296 some debate. The most obvious explanation is that reducing the 295 active inhibition of cortical inputs from the amblyopic eye allows 294 for latent binocular function to be realized. Based on what we 293 know about the excitatory and inhibitory circuits involved in 292 binocular combination, the obvious site of this inhibition would 291 be the point at which contralateral inhibitory signals contribute 290 to contrast gain control prior to excitatory binocular combination 289 (Meese, Georgeoson, & Baker, 2006; Meese & Hess, 2004). This is 288 shown in schematic form in Fig. 7, which depicts the first stage of a two-stage contrast gain control system. However other expla- 287 nations include contrast attenuation of the information from the 286 amblyopic eye and synaptic metaplasticity.  

3.2.1. Signal inhibition

Support for an active inhibitory process comes mainly from the 314 physiological literature. Mower et al. (1984) showed that the 313 binocularity of over 50% of cortical neurons in strabismic cats could 312 be restored with microiontophoretic injections of bicuculline, a 311 GABA antagonist. Furthermore, primate studies have observed 310 non-specific inhibitory interactions between the eyes of strabismic 309 animals (Sengpiel & Blakemore, 1996; Smith et al., 1997) and 308 Sengpiel et al. (2006) showed that strabismic suppression was 307
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, tDCS = transcranial direct current stimulation.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age (yrs)</th>
<th>Tx hours</th>
<th>Amblyopia type</th>
<th>Design</th>
<th>Intervention</th>
<th>Display</th>
<th>Acuity improvement (LogMAR)</th>
<th>Stereopsis improvement</th>
<th>Side effects</th>
<th>Compliance</th>
<th>Treatment location</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults Hess, Mansouri, and Thompson (2010)</td>
<td>9</td>
<td>24–49</td>
<td>5–52</td>
<td>Strab, mixed</td>
<td>Prospective case series</td>
<td>Dichoptic global motion</td>
<td>Stereoscope</td>
<td>0.26 (p = 0.003)</td>
<td>8/9 improved (p = 0.01)</td>
<td>None</td>
<td>Supervised</td>
<td>Laboratory</td>
<td>N/A</td>
</tr>
<tr>
<td>To et al. (2011)</td>
<td>9</td>
<td>17–51</td>
<td>6–35</td>
<td>Aniso, strab, mixed</td>
<td>Prospective case series</td>
<td>Falling blocks</td>
<td>iPod (lenticular)</td>
<td>0.19 (p = 0.02)</td>
<td>5/9 improved (p = 0.04)</td>
<td>None</td>
<td>Supervised</td>
<td>Laboratory</td>
<td>N/A</td>
</tr>
<tr>
<td>Li et al. (2013)</td>
<td>18</td>
<td>19–26</td>
<td>10</td>
<td>Aniso, strab, mixed</td>
<td>Patching controlled, crossover</td>
<td>Falling blocks</td>
<td>Video goggles</td>
<td>0.18 (p &lt; 0.001)</td>
<td>15/18 improved (p &lt; 0.001)</td>
<td>None</td>
<td>Supervised</td>
<td>Laboratory</td>
<td>Stable at 3 months (n = 5)</td>
</tr>
<tr>
<td>Spiegel et al. (2013)</td>
<td>16</td>
<td>17–31</td>
<td>11</td>
<td>Aniso, strab, mixed</td>
<td>Sham controlled, crossover for tDCS, Dichoptic treatment consistent across groups</td>
<td>Falling blocks + tDCS</td>
<td>iPod (lenticular)</td>
<td>0.34 (p &lt; 0.001)</td>
<td>14/16 improved (p = 0.004)</td>
<td>None</td>
<td>Supervised</td>
<td>Laboratory</td>
<td>Stable at 3 months (n = 8)</td>
</tr>
<tr>
<td>Children Hess et al. (2014)</td>
<td>14</td>
<td>13–50</td>
<td>22–108</td>
<td>Aniso, strab, mixed</td>
<td>Prospective case series</td>
<td>Falling blocks</td>
<td>iPod (lenticular or anaglyphic)</td>
<td>0.11 (p &lt; 0.001)</td>
<td>11/14 improved (p &lt; 0.001)</td>
<td>Transient asthenopia</td>
<td>N = 1 patient for 4 h at a time</td>
<td>School lunch break</td>
<td>N/A</td>
</tr>
<tr>
<td>Children Knox et al. (2012)</td>
<td>14</td>
<td>5–14</td>
<td>5</td>
<td>Aniso, strab, mixed</td>
<td>Prospective case series</td>
<td>Falling blocks</td>
<td>Video goggles</td>
<td>0.09 (p &lt; 0.001)</td>
<td>7/14 improved (p = 0.02)</td>
<td>None</td>
<td>Supervised</td>
<td>School (lunch break)</td>
<td>N/A</td>
</tr>
<tr>
<td>Children Li et al. (2014)</td>
<td>45</td>
<td>4–12</td>
<td>16–32</td>
<td>Aniso, strab, mixed</td>
<td>Sham controlled</td>
<td>4 dichoptic games including falling blocks</td>
<td>iPad (anaglyphic)</td>
<td>0.08 (p &lt; 0.001)</td>
<td>5/45 improved (p &gt; 0.05)</td>
<td>None</td>
<td>34/45 played for 4 h or more</td>
<td>Home</td>
<td>Stable at 3 months (n = 21)</td>
</tr>
<tr>
<td>Children Birch et al. (2014)</td>
<td>45</td>
<td>3–7</td>
<td>16–32</td>
<td>Aniso, strab, mixed</td>
<td>Sham controlled</td>
<td>4 dichoptic games including falling blocks</td>
<td>iPad (anaglyphic)</td>
<td>0.09 (p &lt; 0.001)</td>
<td>3/45 improved (p = 0.2)</td>
<td>Not significant</td>
<td>Compliant only: 0.14 (p &lt; 0.001)</td>
<td>Home</td>
<td>N/A</td>
</tr>
</tbody>
</table>
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...
The dichoptic influence from the amblyopic to the fixing eye is to a simple attenuation explanation. In some cases, the strength of gest that there are other forms of interaction that are not amenable to anisometropic amblyopia as well as some with strabismic amblyopia (Harrad & Hess, 1992). However, Harrad and Hess’ results suggested 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. 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).](image)

![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 on 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).](image)

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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
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 electric 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, 2008). 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 stimulation 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.

Our first study in a small group of adults with amblyopia supported this hypothesis; both excitatory and inhibitory rTMS protocols increased ambylopic 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 (rTBS), a form of rTMS that requires only a short stimulation period) over 5 days led to...
In a parallel series of studies, we have investigated the effect of 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 eye. 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 (Barbies 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 still 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
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).

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