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**Binocular vision in amblyopia: structure, suppression and plasticity**

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## Binocular vision in amblyopia: structure, suppression and plasticity

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### Abstract

The amblyopic visual system was once considered to be structurally monocular. However, it is now evident that the capacity for binocular vision is present in many observers with amblyopia. This has led to new techniques for quantifying suppression that have provided insights into the relationship between suppression and the monocular and binocular visual deficits experienced by amblyopes. Furthermore, new treatments are emerging that directly target suppressive interactions within the visual cortex and, on the basis of initial data, appear to improve both binocular and monocular visual function, even in adults with amblyopia. The aim of this review is to provide an overview of recent studies that have investigated the structure, measurement and treatment of binocular vision in observers with strabismic, anisometropic and mixed amblyopia.

### 1 General introduction

Amblyopia is a neuro-developmental disorder of the visual cortex that occurs when binocular visual experience is disrupted during early childhood. The disorder is usually diagnosed on the basis of reduced visual acuity in an otherwise healthy eye<sup>1</sup>. However, amblyopia is characterized by a range of visual deficits that affect both monocular and binocular visual function<sup>2</sup>. For many years these deficits were interpreted within a framework assuming that amblyopes are anatomically monocular and that any residual binocular interactions were purely suppressive and secondary to the loss of monocular function. However, recent findings have provided strong evidence for intact binocular processes in adult amblyopes that may have appeared to have been lost but were, in reality, suppressed under binocular viewing conditions. Furthermore, current evidence indicates that suppression plays a primary role in both the binocular and monocular deficits experienced by patients with amblyopia. These findings have led to new approaches to the treatment of amblyopia that target suppressive interactions within the visual cortex. Here we review studies indicating that binocular function is present in amblyopia and describe the techniques that have been developed to quantify suppression in patients with amblyopia. We also present combined data from studies investigating the use of novel treatments that target suppressive interactions within the amblyopic visual cortex.

## 2 Inferring the architecture of the amblyopic visual system

In this section, we summarise results indicating that the amblyopic visual system has the capacity for binocular vision and the architectures of computational models that are based upon these results.

### 2.1 Binocular summation

A common measure of binocular function is to assess the improvement on a particular task when the stimuli are presented to two eyes, rather than one. For detection of low contrast grating stimuli the binocular improvement is about a factor of 1.4-1.8 in normal observers<sup>3,4</sup>. This 'binocular summation' is beyond that expected for probabilistic combination of two independent inputs, and so implies the existence of physiological mechanisms that integrate information from the two eyes.

In amblyopia, binocular summation is typically reported as being absent or greatly reduced<sup>5-8</sup>. Many researchers concluded from this that binocular combination simply did not occur in amblyopes, consistent with early physiological work on cats with surgically induced strabismus<sup>9</sup>. But there is an alternative explanation. Because contrast sensitivity is greatly reduced in the amblyopic eye, perhaps it simply provides too little drive to produce a measurable contribution in standard summation experiments. If the signal to the amblyopic eye were boosted, might normal levels of binocular summation occur?

This possibility was tested by Baker et al.<sup>10</sup>, who adjusted the contrast of the stimulus presented to the amblyopic eye so that it was as strong (relative to its own detection threshold) as the stimulus presented to the fellow eye. This procedure yielded normal levels of binocular summation, providing strong evidence that amblyopes retain binocular mechanisms. This surprising result provided a foundation for treatments designed to recover the latent binocular capacity of amblyopes (section 3). But what is the cause of the reduced sensitivity of the amblyopic eye? The following sections discuss a number of masking studies that have addressed this question.

### 2.2 Pedestal masking

A longstanding proposal to explain reduced sensitivity in amblyopia is an active process of suppression from the fellow eye. Several studies have attempted to measure this using a dichoptic pedestal masking paradigm, where a high contrast mask in one eye impedes detection of similar target patterns shown to the other eye. Early work<sup>6</sup> concluded that interocular suppression was normal in amblyopia, because dichoptic masking functions did not differ substantially between amblyopic and normal observers. However, these authors tested very few subjects, so their results may not be generally applicable.

Harrad and Hess<sup>11</sup> repeated the experiment on a larger number of amblyopes with varying aetiologies. Some of their results resembled those of

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2  
3 the previous study<sup>6</sup>, but they also found evidence for stronger masking from  
4 the fellow to the amblyopic eye, and weaker masking in the opposite direction.  
5 These findings support the notion that some amblyopes exhibit abnormal  
6 suppression of the affected eye. A more recent study<sup>12</sup> that examined  
7 strabismic amblyopes found either normal or weaker-than-normal suppression  
8 of the amblyopic eye for this type of task. This difference could be due to the  
9 heterogeneity of amblyopic symptoms, or might be due to methodological  
10 differences between the studies. We will discuss the implications of these  
11 findings in section 2.5 below.  
12

13  
14 An alternative to dichoptic presentation is to display the pedestal and target to  
15 the same eye. The task then becomes one of increment detection, and  
16 produces a characteristic 'dipper' function. Bradley and Ohzawa<sup>13</sup> compared  
17 dipper functions in the two eyes of a pair of amblyopes, and found an upward  
18 and rightward shift, such that masking was increased even at high pedestal  
19 contrasts (a similar result has been reported at higher spatial frequencies<sup>14</sup>).  
20 This intriguing finding (since confirmed<sup>12</sup>) implies that internal noise is  
21 increased in the amblyopic eye (i.e. its responses are more variable)  
22 compared with the fellow eye. This is because, unlike increases in  
23 suppression that shift the dipper diagonally (causing the dipper handles to  
24 superimpose, see<sup>15</sup>), a vertical shift is produced only by changing the signal  
25 to noise ratio<sup>16</sup>. If noise is increased in the amblyopic eye, this could be  
26 assessed directly using the noise masking paradigm (e.g.<sup>17</sup>). The next  
27 section summarises studies that have attempted this.  
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### 30 31 2.3 Noise masking in amblyopia 32

33 By adding external noise to a stimulus, an estimate of the internal noise in the  
34 detecting channel can be obtained when the external noise is of sufficient  
35 contrast to raise detection thresholds<sup>17</sup>. Several studies have applied this  
36 paradigm to compare the level of internal noise across amblyopic and fellow  
37 eyes within individual observers. One such study<sup>18</sup> found clear evidence for  
38 increased internal noise in two of their four observers, with the remaining two  
39 observers showing a pattern more consistent with poor information extraction  
40 (calculation efficiency). For letter identification though, little increase in internal  
41 noise was found, but much poorer calculation efficiency was evident<sup>19</sup>.  
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44 External noise studies using more sophisticated techniques (e.g. classification  
45 image and double pass methods) have also concluded that internal noise is  
46 elevated in the amblyopic eye<sup>20-22</sup> though it is unclear whether this is additive,  
47 multiplicative or both<sup>12, 21</sup>. Increased noise at the psychophysical level might  
48 be caused by fewer active neurons (leading to lower signal to noise ratios) or  
49 inappropriate connections between neural populations. Evidence favouring  
50 the latter possibility was reported<sup>23</sup>, though this conclusion was based in part  
51 on the lack of a difference in contrast discrimination performance between  
52 amblyopic and fellow eyes in their observers. As detailed in section 2.2, other  
53 studies have found a substantial difference on this task<sup>12-14</sup>, so both  
54 explanations may be correct.  
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### 57 2.4 Perceived phase and perceived contrast 58 59 60

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4 A recent body of work has extended a paradigm developed by Ding and  
5 Sperling<sup>24</sup> to investigate amblyopia<sup>25-27</sup>. Observers are presented with two  
6 gratings, shown separately to each eye with variable phases and contrasts  
7 (Figure 1). They are required to judge the perceived phase (and sometimes  
8 also perceived contrast) of the resulting binocular percept. Amblyopes show  
9 various abnormal behaviours on this task, consistent with a reduction in the  
10 weight given to the signal in the amblyopic eye, and sometimes with additional  
11 suppression from the fellow eye (see section 2.5). However, a critical point  
12 demonstrated by this paradigm is that amblyopes do not respond as though  
13 they see only the image shown to the fellow eye, or the amblyopic eye, in  
14 isolation. This supports the idea that they are able to integrate information  
15 binocularly, despite the signals from the amblyopic eye being degraded in  
16 various ways. So, amblyopes do have a form of binocular single vision,  
17 consistent with the finding of a binocular advantage at detection threshold<sup>10</sup>.  
18 This realisation has prompted the development of several computational  
19 models of amblyopia.  
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## 23 2.5 Models of amblyopia

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25 Baker et al.<sup>12</sup> took a model developed to explain normal binocular  
26 combination<sup>4</sup> and asked how it needed to be changed to account for the  
27 pattern of contrast discrimination functions measured from 8 strabismic  
28 amblyopes. They considered several 'lesions' to the model, including absent  
29 binocular combination, and suppression from the fellow eye onto the  
30 amblyopic eye. Surprisingly, these two modifications were unable to account  
31 for any of the key features of the data. Instead, a very different picture  
32 developed of the architecture of the amblyopic visual system. In the most  
33 successful model, binocular combination and interocular suppression are  
34 normal. However, the input to the amblyopic eye is attenuated at an early  
35 stage, and subject to increased levels of noise. These two small modifications  
36 correctly predicted all of the main findings from that study. However the fact  
37 that increased suppression was not required was a consequence of the  
38 pedestal masking paradigm used in this study and does not imply that it is  
39 absent.  
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43 Huang et al.<sup>26, 27</sup> made similar modifications to the binocular model of Ding  
44 and Sperling<sup>24</sup> to account for their phase and contrast matching data in  
45 amblyopes. They confirmed the importance of monocular attenuation with  
46 intact binocular combination, and also found evidence for increased  
47 interocular suppression. Ding et al.<sup>25</sup> made further refinements to the gain  
48 properties of this class of model to account for several subtle patterns in their  
49 data.  
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## 52 2.6 Interim summary

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54 We can extrapolate from these studies some general points about contrast  
55 vision in amblyopia. First, binocular mechanisms do appear to exist in the  
56 human amblyope, and involve both summation and suppression of signals  
57 across the eyes. But the amblyopic signal is weaker, noisier, and may be  
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3 strongly suppressed by signals in the fellow eye. These factors combine so  
4 that, for typical high contrast scenes, most of the information available to the  
5 observer comes from the fellow eye. So, amblyopes can be *structurally*  
6 binocular, yet appear *functionally* monocular, in that they base their responses  
7 in natural viewing tasks on the input from the fellow eye.  
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### 9 10 3. Suppression

#### 11 12 3.1 History

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14 As described above, suppression within the context of binocular vision refers to  
15 an inhibitory influence of the fellow eye over the amblyopic eye when both  
16 eyes are viewing. It has been assumed that the role of suppression is to stop  
17 information from the amblyopic eye reaching perception to prevent visual  
18 confusion or diplopia. However, evidence for this assumption within clinical  
19 research is mixed at best. Initially in the 1950s and 1960s suppression was a  
20 hot topic and the work of Travers<sup>28</sup> in Melbourne, Pratt-johnson<sup>29</sup> in the UK  
21 and Jampolski<sup>30</sup> in the USA stand out. They carefully plotted suppression  
22 scotomata and related their size and position in different forms of strabismus.  
23 There was a consensus that the scotomata were localized and involved the  
24 region of the visual field in the deviated eye that corresponded to the fovea in  
25 the fixing eye, sometimes extending to include the foveal region of the  
26 deviating eye. In the following 3 decades, interest in suppression waned and  
27 while its presence may have been documented in clinical examinations, not  
28 much use was made of it. More recently, there has been a revival in research  
29 into suppression which involves new and much less dissociative ways of  
30 measuring it<sup>31-33</sup> and treatment interventions which directly target  
31 suppression (described in section 4). For many, suppression is the enemy in  
32 terms of restoring binocular function and its elimination is a necessary first  
33 step in any binocular therapy<sup>34-36</sup>. For others who worry about the possibility  
34 of producing diplopia, suppression is their friend, ensuring that when both  
35 eyes are open there is only vision from one eye. In a lot of ways we are still in  
36 the dark ages when it comes to suppression, opinions rage for and against its  
37 elimination, but little evidence is furnished to support either camp. The  
38 renaissance in thinking about suppression only came when we developed a  
39 means of numerically quantifying its strength. Once we had a number, rather  
40 than a binary on/off measure, we could ask questions that are addressed in  
41 detail below such as; *how does suppression vary in amblyopia?, how is*  
42 *suppression distributed across the visual field? Is suppression similar in*  
43 *strabismics and ansiometropes?, and how can we modulate suppression?*  
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50 3.1. Methods of measuring suppression. Understanding of suppression has  
51 been impeded by the lack of quantitative measures as most clinical tests,  
52 such as the Worth 4 Dot test, only indicate whether suppression might or might  
53 not be present. Recently, a number of different tests have been devised, two  
54 based on global processing (form and motion) and another involving local  
55 phase and contrast (Figure 1).  
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3 3.1.1. The motion coherence test (Figure 1A). This test involves the dichoptic  
4 presentation of noise elements (having a random motion direction) to one eye  
5 and signal elements (having the same coherent motion direction) to the other  
6 eye<sup>37</sup>. The noise presented to one eye makes it more difficult to detect the  
7 direction of the signal in the other eye. In binocularly normal individuals with  
8 no strong dominance, it does not matter which eye sees the signal and which  
9 eye sees the noise; the dichoptic interactions are balanced<sup>38</sup>. However, this  
10 is no longer the case in amblyopes. Owing to suppression, performance is  
11 better when the noise is presented to the “suppressed” amblyopic eye and  
12 worse when signal is in the amblyopic eye. Suppression can be measured by  
13 assessing how much the contrast of the stimulus presented to the fellow fixing  
14 eye has to be reduced to reach a point where it does not matter which eye  
15 sees the signal and which sees the noise, task performance is equal. This can  
16 only occur when information from the two eyes is combined equally and,  
17 being a global motion task, this approach involves an assessment of  
18 suppression which relies on dorsal extra-striate function. In the original  
19 version<sup>37</sup> of this technique, blocks of signal to one eye and noise to the other  
20 eye were presented using randomly interleaved staircases. An abbreviated  
21 version involves the presentation of signal to the amblyopic eye and noise of  
22 variable contrast to the fellow eye<sup>39</sup>. More recently, we have devised a  
23 version of the test specifically for high anisometropes in which dot size is  
24 randomized to ensure that anisokenia does not provide a cue for signal noise  
25 segregation<sup>40</sup>.

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30 3.1.2. The orientation coherence test (Figure 1B). This test is identical in  
31 principle to that described above for motion coherence but uses a task  
32 involving orientation coherence<sup>41</sup> that has been adapted<sup>42</sup> for dichoptic  
33 presentation. The motivation was to assess suppression using a task that  
34 relies on the ventral extra-striate cortex.

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36 3.1.3. The phase test (Figure 1C). In this test, also referred to in section 2.4,  
37 the two eyes view suprathreshold sinusoidal gratings of equal but opposite  
38 spatial phase (e.g.  $-45^\circ$  and  $+45^\circ$ ). If the fused percept has an equal  
39 contribution from each eye then the perceived phase will be at the arithmetic  
40 sum of each eye’s phase (i.e. 0). The interocular contrast can be manipulated  
41 and the phase in the fused percept measured to ascertain the degree of any  
42 binocular imbalance (i.e. suppression). Typically a low spatial frequency of  
43 0.3c/d is used and the perceived phase is measured using a thin line aligned  
44 to the peak of the waveform<sup>24, 26</sup>.

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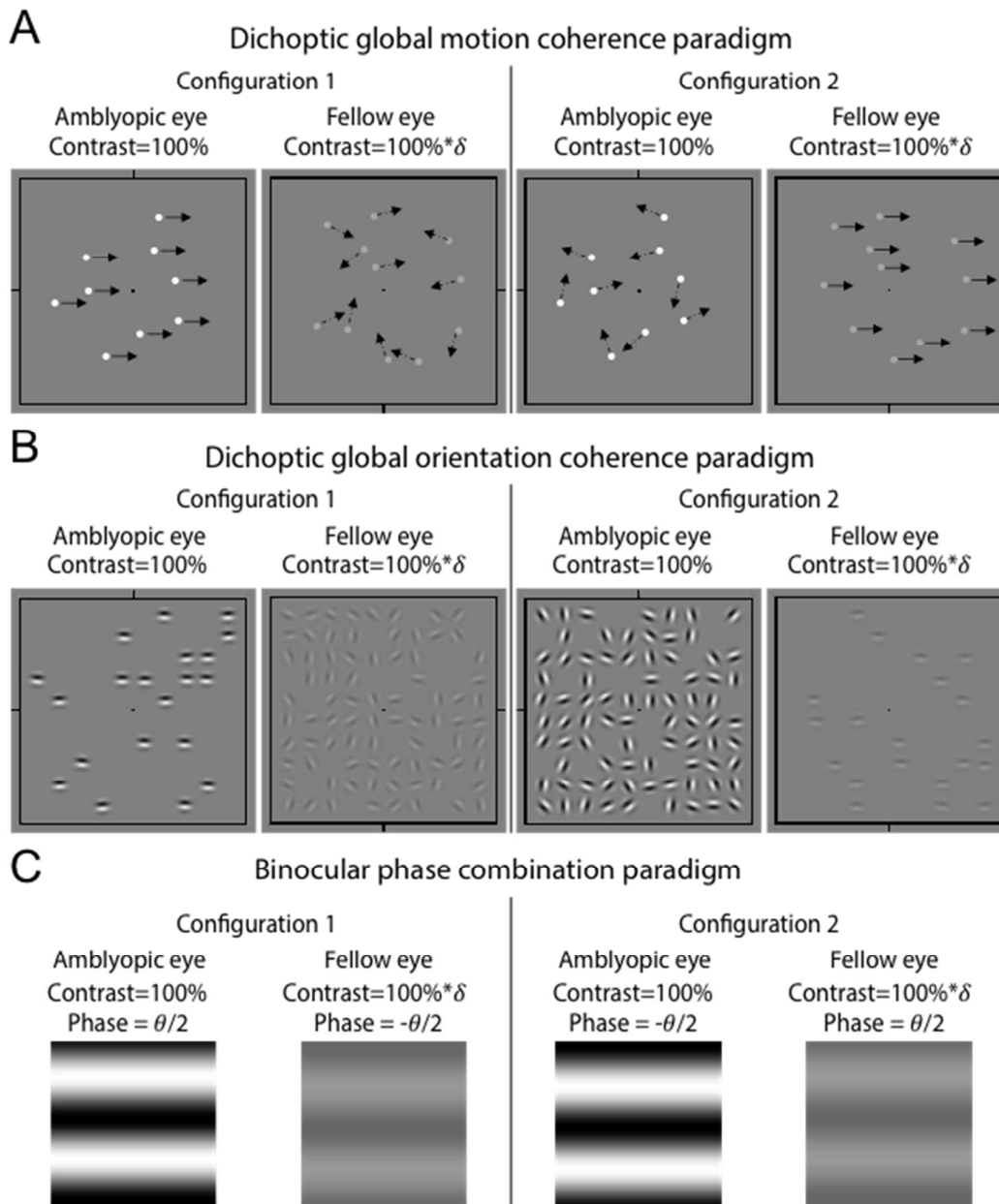


Figure 1. An illustration of the stimuli and paradigms used to measure interocular suppression. (A) The dichoptic global motion coherence paradigm. (B) The dichoptic global orientation coherence paradigm. (C) The binocular phase combination paradigm. See sections 3.1.1 to 3.1.3 for further details.

### 3.2 Suppression and amblyopia

Until recently it was widely accepted that suppression was inversely related to the depth of amblyopia and that the nature of suppression differed fundamentally between strabismic and anisometropic amblyopes. Evidence

for the inverse relationship between suppression and the depth of amblyopia came from earlier laboratory work<sup>43</sup> which involved 9 patients of whom 1/3 were alternating strabismics. Alternating strabismics typically have suppression (which may be very strong<sup>44</sup>) but no amblyopia and therefore are distinct from strabismic amblyopes. The alternators within the sample of patients examined in the earlier study biased the correlation in the negative direction. More recently, Li et al<sup>45</sup> undertook a study of suppression using the motion coherence test described above on a much larger sample of amblyopes with constant strabismus, anisometropia or both. Figure 2 shows the strength of suppression quantified as the fellow eye contrast at which normal binocular combination occurred (lower contrast = stronger suppression) as a function of letter acuity difference between the amblyopic and fellow eyes. There is a comparable degree of suppression in the anisometropic and strabismic populations (although individuals differ) and stronger suppression is associated with a greater acuity deficit (the sloping solid line is the best linear fit to the data). Other studies have now corroborated this result<sup>42, 46, 47</sup>.

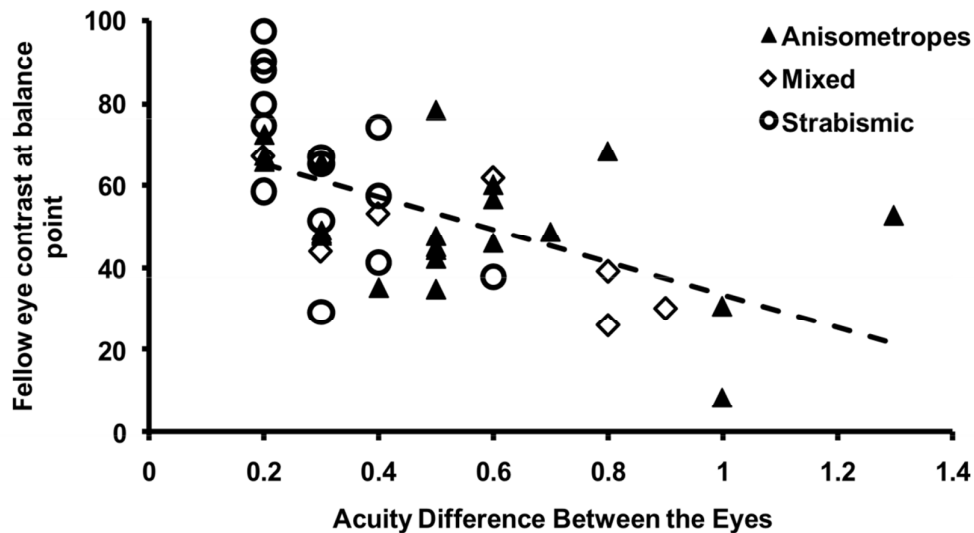
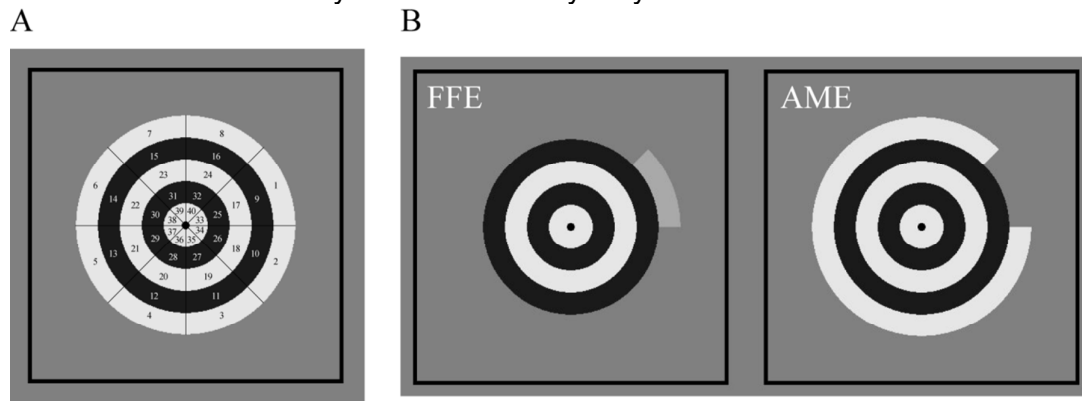


Figure 2. Mean fellow eye contrast at balance point as a function of interocular acuity difference (Log MAR) for 43 patients with amblyopia. Lower values on the Y axis indicate stronger suppression (see section 3.2 for details). There was a significant negative correlation ( $p < 0.001$ ) indicating that stronger suppression was associated with greater acuity loss in the amblyopic eye. Figure reproduced from<sup>45</sup>.

### 3.3. The regional distribution of suppression

Since the work of Travers<sup>28</sup>, Jampolski<sup>30</sup> and Pratt-Johnson<sup>29, 48</sup>, the word scotoma has always been synonymous with suppression. This early work using handheld perimetric techniques argued for the existence of well-localized regions of suppression strategically located in the amblyopic visual field as described above. We recently developed a novel means<sup>49</sup> of measuring the regional extent of suppression within the central 20° of the

visual field and re-investigated this issue. The stimulus is shown in Figure 3 and a summary of the results in Figure 4. The measurement involves dichoptic contrast matching of different segments of dichoptically presented annuli. The results shown in Figure 4 suggest that while suppression extends throughout the central 20°, it is greater in the central region. The overall magnitude and regional distribution of suppression appears to be similar in strabismic and anisometropic amblyopia. We found no evidence of localized islands of suppression, though it must be pointed out that the spatial resolution of our test may have missed any very fine structure.



**Figure 3.** The annular-based suppression mapping stimulus. Panel A depicts the 40 regions of the visual field that were tested. The radius of the most eccentric ring is 10°. Panel B depicts the dichoptic testing arrangement. One segment was shown to the fellow eye and the remaining segments from the same annulus were shown to the amblyopic eye. The observer varied the luminance of the segment with respect to the mean background luminance (i.e. contrast) shown to the fellow eye to match the perceived contrast of the segments from the same annulus shown to the amblyopic eye. The remaining annuli were shown to both eyes at 80% contrast. Figure from<sup>49</sup>.

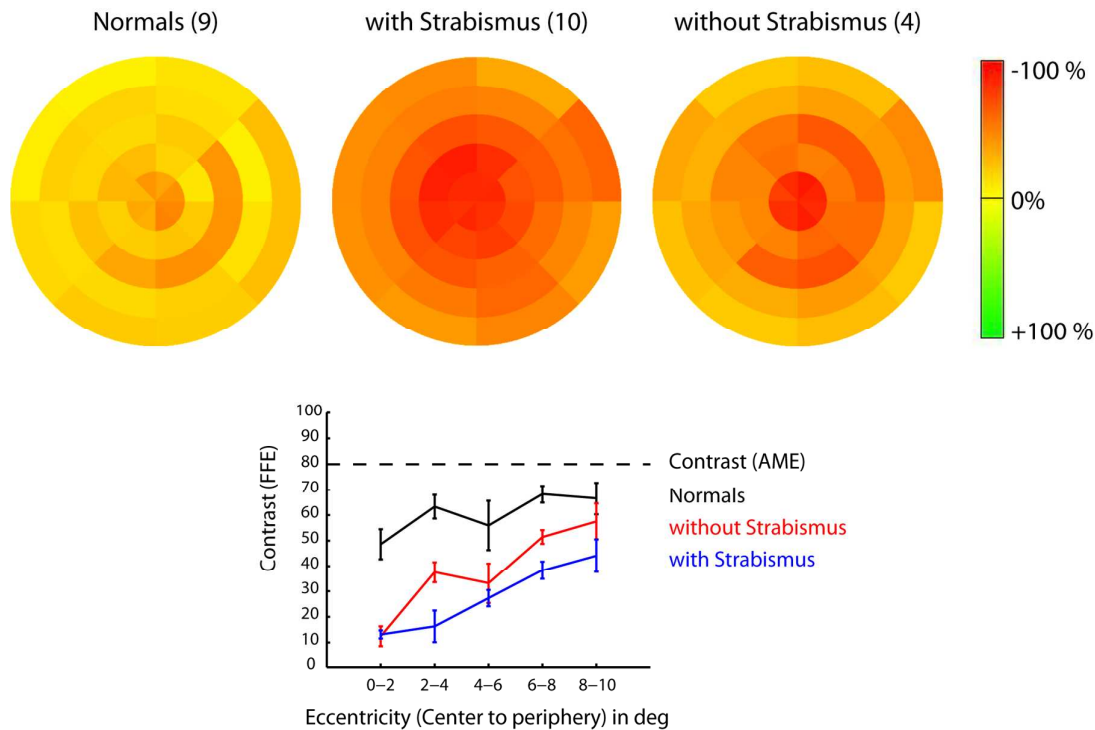


Figure 4. Average suppression maps for observers with normal binocular vision ( $n = 10$ ) and amblyopes with ( $n = 10$ ) and without ( $n = 4$ ) strabismus. Amblyopia is associated with significantly stronger suppression than that found in normals. The color maps indicate the magnitude and extent of suppression across the central field, the graphs the average suppression for each population. Figure from <sup>49</sup>.

### 3.4. Modulating suppression

#### 3.4.1 Short-term monocular occlusion

Short-term (e.g. 2.5hrs) monocular occlusion in observers with normal vision can alter the balance of binocular interactions. Once the occluding patch is removed, the contribution from the previously patched eye to the binocular percept increases. This was first shown using binocular rivalry<sup>50</sup> whereby the image shown to the previously patched eye becomes dominant. We investigated this effect further<sup>51</sup> using the motion coherence test<sup>37</sup>, the phase test<sup>26</sup> and the dichoptic contrast test<sup>26</sup> and found good support for this novel phenomenon. Examples of the results for the phase and motion coherence tests are shown in Figure 5.

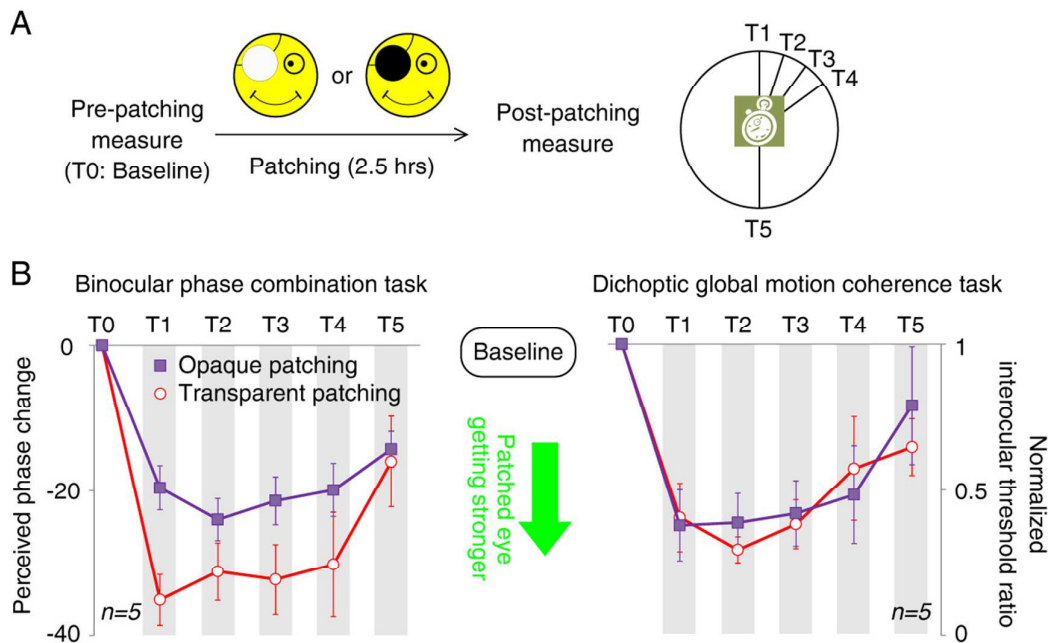


Figure 5. The effect of 2.5 hrs of monocular occlusion with either a light-tight patch or a diffuser on the binocular phase combination task and the dichoptic global motion coherence task. (A) Experimental protocol, (B) Patching effects on the binocular phase combination task (left panel) and dichoptic global motion coherence task (right panel). Error bars represent standard errors. Figure from<sup>51</sup>.

Although the effect is temporary, lasting only 30 minutes, it is robust and involves both the primary and extra-striate visual cortex because motion coherence is more of an extra-striate function than contrast or phase matching. Although the mechanism is not well understood, it must involve binocular processes because if one measures monocular contrast thresholds after patching, the threshold of the previously patched eye drops while the threshold of the unpatched eye increases, reflecting a reciprocal (i.e. binocular) effect<sup>51</sup>.

Comparable effects can also be seen in amblyopes, whereby if the amblyopic eye is patched (the opposite of traditional patching therapy) then the amblyopic eye's subsequent contribution to the binocular percept is strengthened. A comparison of the effects of short-term occlusion in normals and amblyopes on the phase test is shown in Figure 6.

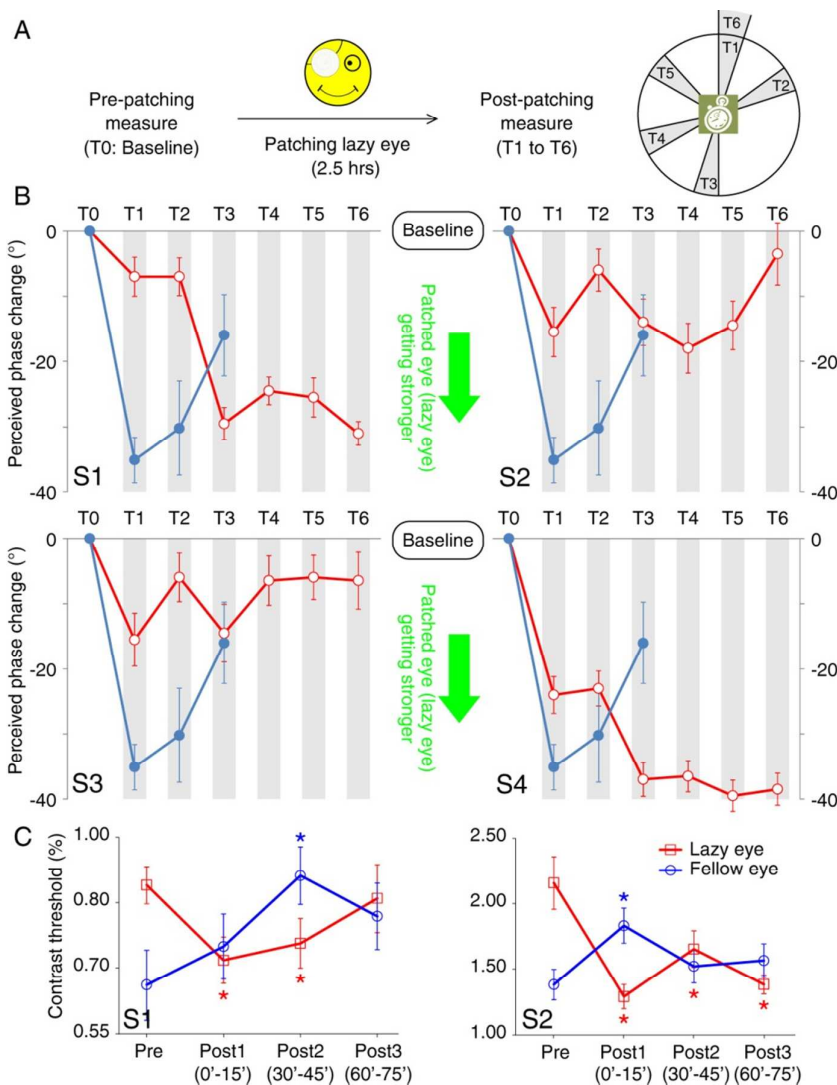


Figure 6. a) The time line of the patching and testing protocol. b) Measurement of binocular balance using the phase test after patching of the amblyopic eye for each of 4 observers with amblyopia (S1-S4). The red lines with open dots in each panel represent the time course of the perceived phase change for each amblyopic observer, the blue lines and filled dots represent the average results of five normal controls after patching of one randomly selected eye. Displacement below the baseline represents a strengthening of the patched eye's contribution to the binocular percept. Error bars represent standard errors. c) contrast threshold changes as a result of the above patching protocol.

The time course of the strengthening effect shown in Figure 6 is different in normals and amblyopes. In amblyopes it appears to be more sustained; compare the effects at the time point T3, where the effect is seen to be reducing for normals but increasing for amblyopes. Contrast thresholds are affected in a reciprocal manner with the previously patched eye having lower thresholds and the unpatched eye exhibiting higher thresholds on removal of the patch (Figure 6C). This approach, the opposite of traditionally occlusion therapy, may offer hope as a means of improving binocular function in

amblyopes by redressing the imbalance cause by chronic suppression. It also suggests that patching therapy may increase suppression by inadvertently strengthening the fellow eye. If this is so we are left with an interesting conundrum; *how do we explain the improvement in acuity coexisting with increasing suppression that may occur after standard occlusion therapy?*

### 3.4.2 Other means of modulating suppression

Suppression can be modulated in a variety of ways that involve reducing the drive from the fellow eye. For example, optical blur, neutral density filters and Bangerter filters placed over the fellow eye will result in less suppressive drive and hence a more balanced binocular outcome. Figure 7 shows how neutral density filters, which change mean luminance but not contrast, affect binocular combination in a population of observers with normal binocular vision<sup>52</sup>.

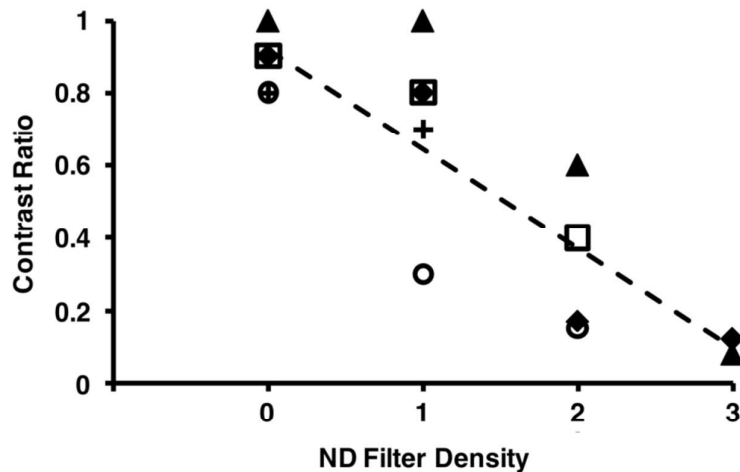


Figure 7. The contrast ratio between the eyes on the dichoptic global motion coherence task as a function of the strength of neutral density filter placed over the non-dominant eye for observers with normal binocular vision. A ratio of 1 on the Y-axis indicates normal binocular combination. Lower ratios indicate that greater contrast has to be presented to the eye with the ND filter for normal binocular combination to be achieved. The dashed line is the best linear fit and shows that greater ND filter strengths require greater contrast imbalances to achieve normal binocular combination. Each symbol represents a different observer. From<sup>52</sup>.

Figure 7 shows measurements of binocular balance in terms of the contrast ratio for the signal and noise within the dichoptic motion coherence task<sup>37</sup>. A contrast ratio of unity indicates balanced weights for each eye's input for binocular vision. Results are shown for different subjects, the denser the filter in front of one eye, the more the balance shifts in favour of the unfiltered eye. Lens blur and Bangerter filters have similar effects<sup>53</sup>. Similarly, in amblyopia where there is an initial imbalance of the inputs of the two eyes due to

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3 suppression, lens blur, neutral density filters or Bangerter filters could  
4 potentially be used in front of the sighted eye to reduce suppression and re-  
5 balance the inputs of the two eyes<sup>53, 54</sup>. However there is more to consider  
6 than just suppression because removal of suppression is a necessary but not  
7 sufficient step for restoring functional binocular vision (i.e. stereopsis). Both  
8 neutral density filters and Bangerter filters are less than ideal choices when it  
9 comes to stereoscopic function<sup>53</sup>. The way in which they affect the signal  
10 emanating from the sighted eye turns out to be particularly detrimental for  
11 stereopsis. Neutral density filters introduce a temporal filtering and delaying  
12 of the visual response (Renaud, Zhou and Hess, forthcoming) which reduces  
13 the temporal correlation needed for stereoscopic function. Bangerter filters  
14 are composed of randomly arranged micro-particles which result in a spatial  
15 decorrelation of the images in the two eyes therefore fundamentally reducing  
16 stereo processing<sup>53</sup>. Lens blur which simply reduces the contrast in a spatial  
17 frequency dependent fashion (i.e. more so at high spatial frequencies) is the  
18 best of the three types of partial occlusion as it still supports stereopsis for low  
19 spatial frequencies (i.e. coarse disparities)<sup>53</sup>.

### 22 3.5 Interim summary

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25 Suppression can be measured using a variety of techniques that allow for the  
26 contribution of each eye to the binocular percept to be quantified. Using such  
27 techniques it has been shown that stronger suppression is associated with  
28 greater visual dysfunction in amblyopia and that suppression extends  
29 throughout the central 20° of the visual field in both strabismic and  
30 anisometropic amblyopia. Suppression can be modulated in both observers  
31 with normal binocular vision and amblyopes using ND filters, optical blur and  
32 Bangerter filters, however only optical blur is permissive for stereopsis. In  
33 addition, recent data indicate the occlusion of one eye results in a subsequent  
34 strengthening of that eye's contribution to binocular combination. This  
35 provides a new possibility for amblyopia treatment which is the topic of the  
36 next section.  
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### 39 4. Suppression as a target for amblyopia treatment

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42 Evidence presented in the preceding sections supports the idea that  
43 individuals with amblyopia have the capacity for binocular vision, but that this  
44 capacity is suppressed under normal viewing conditions. Furthermore, it  
45 appears that suppressive or inhibitory interactions within the visual cortex may  
46 play a central role in the loss of both monocular and binocular vision that  
47 characterizes amblyopia. Stronger suppression is associated with poorer  
48 stereopsis and poorer amblyopic eye visual acuity in humans<sup>40, 45-47</sup> and  
49 compelling links between suppression and visual dysfunction have been  
50 found in animal models of amblyopia and strabismus<sup>55, 56</sup>. Initial evidence  
51 also indicates that stronger suppression is associated with a poorer response  
52 to occlusion therapy in children<sup>47</sup>, even when factors such as pre-treatment  
53 visual acuity and stereopsis are accounted for<sup>46</sup>. This raises the possibility  
54 that suppression not only masks latent visual capabilities<sup>57</sup> but also gates  
55 visual cortex plasticity<sup>58</sup>. In this context, interventions that directly target  
56 suppressive interactions within the visual cortex may be particularly relevant  
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3 to the treatment of amblyopia. New treatments for amblyopia are highly  
4 desirable as current treatments, whilst effective at improving amblyopic eye  
5 acuity, are not ideal (see <sup>59</sup> for a recent discussion of the issues involved).  
6

#### 7 8 4.1 Non-invasive brain stimulation and amblyopia

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10 Non-invasive brain stimulation techniques can be used to modulate  
11 fundamental properties of neural systems such as excitation and inhibition <sup>60</sup>.  
12 These techniques have been intensively studied in the context of neuro-  
13 rehabilitation as abnormal patterns of inhibition and excitation have been  
14 implicated in a wide range of neurological disorders. For example, beneficial  
15 effects of non-invasive brain stimulation have been reported for disorders  
16 such as depression, stroke, tinnitus, Parkinson's disease and chronic pain <sup>61-</sup>  
17 <sup>65</sup>. The two most prevalent forms of non-invasive brain stimulation are  
18 transcranial magnetic stimulation (TMS) and transcranial direct current  
19 stimulation (tDCS). TMS involves the generation of brief, targeted magnetic  
20 fields which pass harmlessly through the scalp and generate a weak electrical  
21 current in the underlying region of cortex <sup>16, 66</sup>. When multiple pulses of TMS  
22 are administered in close succession, either as a train of pulses (a technique  
23 known as repetitive TMS or rTMS <sup>67</sup>) or a series of "bursts" (e.g. theta burst  
24 stimulation or TBS <sup>68</sup>), the stimulation can transiently alter excitation and  
25 inhibition within the stimulated region. tDCS involves the use of a weak (1 or 2  
26 mA) direct current passed between two large head-mounted electrodes  
27 positioned over the brain regions to be stimulated. Cathodal stimulation tends  
28 to decrease excitability of the stimulated neural population whereas anodal  
29 stimulation often has the opposite effect <sup>69</sup>. rTMS, TBS and tDCS are effective  
30 when delivered to the visual cortex modulating factors such as contrast  
31 sensitivity, motion perception, visual evoked potentials and phosphene  
32 thresholds (the intensity of a single pulse of TMS delivered to the occipital  
33 lobe required to induce the percept of a phosphene; a measure of visual  
34 cortex excitability) <sup>70-75</sup>.  
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39 A series of recent studies have investigated the possibility that non-invasive  
40 stimulation of the visual cortex can improve vision in adults with amblyopia <sup>76-</sup>  
41 <sup>79</sup>. The rationale for applying non-invasive brain stimulation to amblyopia is  
42 manifold. Firstly, rTMS, TBS and tDCS have been shown to modulate  
43 abnormal inter-hemispheric patterns of suppression/inhibition within the  
44 human motor cortex suggesting that these techniques can reduce  
45 pathological suppression <sup>62, 80</sup>. Secondly, the effects of brain stimulation have  
46 been shown to interact with ongoing neural activity within the stimulated brain  
47 region. This allows for distinct neural populations to be targeted even when  
48 the populations inhabit the same region of stimulated cortex <sup>81</sup>. In particular,  
49 brain stimulation may act to restore homeostasis to neural populations <sup>82</sup>. This  
50 is relevant to amblyopia as the resolution of brain stimulation does not allow  
51 for separate ocular dominance columns to be targeted, however the  
52 stimulation may differently affect neural inputs from the amblyopic and fellow  
53 eye by virtue of their differing levels of excitation and inhibition (as described  
54 in the sections above). Thirdly, brain stimulation techniques may act to reduce  
55 intra-cortical inhibition <sup>67</sup> which has been strongly implicated as a "break" on  
56 visual cortex plasticity in animal models of amblyopia <sup>83</sup>. Finally, anodal tDCS  
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3 in particular has been shown to reduce GABA levels within the human motor  
4 cortex<sup>84</sup> and behavioral evidence suggests that similar effects may occur  
5 within the human visual cortex<sup>85</sup>. This is of interest in the context of amblyopia  
6 as GABA is thought to play a key role in suppression of inputs from the  
7 amblyopic eye within the visual cortex<sup>56</sup>. We therefore hypothesized that non-  
8 invasive brain stimulation may reduce suppression of inputs from the  
9 amblyopic eye within the visual cortex and/or enhance visual cortex plasticity.  
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11 Current evidence is generally consistent with this hypothesis (Figure 8).  
12 Specifically, we have shown that non-invasive brain stimulation can improve  
13 contrast sensitivity in at least a subset of adults with amblyopia. In the first  
14 study to address this question we measured contrast sensitivity for low and  
15 high spatial frequency Gabor targets (the exact spatial frequency was tailored  
16 for each patient) before and after an inhibitory rTMS protocol (1Hz stimulation,  
17 n = 9 patients) and an excitatory protocol (10Hz stimulation, n = 6 patients)  
18 delivered to the primary visual cortex<sup>79</sup>. Stimulation of the motor cortex was  
19 used as a control condition. Both types of rTMS resulted in significant  
20 improvements in contrast sensitivity (a mean improvement of approximately  
21 40%) when high spatial frequency targets were viewed by the amblyopic eye  
22 (7/9 patients improved for 1Hz and 6/6 for 10 Hz, including the two patients  
23 who did not improve for 1Hz). No improvements were found for the low spatial  
24 frequency target for which the amblyopic eyes did not show a pronounced  
25 contrast sensitivity deficit at baseline. Furthermore, improvements were not  
26 found for the fellow eye after visual cortex stimulation or for either eye after  
27 motor cortex stimulation, indicating that the rTMS effects specifically targeted  
28 amblyopic eye function. The improvements were transient however, with  
29 thresholds returning to baseline within approximately 24 hours after  
30 stimulation. In a follow-up study we investigated the effect of repeated  
31 administration of rTMS (in this case continuous TBS; cTBS) over five  
32 consecutive days in four adults with amblyopia<sup>78</sup>. The acute effects of a single  
33 stimulation session (measured in 5 patients) resulted in improvements in  
34 contrast sensitivity for the amblyopic eye of a similar magnitude to the original  
35 study. Furthermore there was a cumulative effect of cTBS on contrast  
36 sensitivity over the first two sessions which stabilized over subsequent  
37 sessions and endured for up to 78 days.  
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43 Improvements in contrast sensitivity have also been found in a subset of  
44 adults with amblyopia after anodal tDCS of the visual cortex (20 minutes at  
45 2mA)<sup>77</sup>. Of 13 adults tested, 8 showed improvements in amblyopic eye  
46 contrast sensitivity after anodal tDCS (an average of 27% improvement)  
47 whereas 5 showed the opposite effect. No reliable improvements for either  
48 group were found for amblyopic function after cathodal stimulation or for the  
49 fellow fixing eye. Previous studies applying anodal tDCS to other neurological  
50 disorders have also reported groups of responders and non-responders<sup>86</sup>  
51 suggesting that this type of brain stimulation may only be of use for a subset  
52 of participants. To ensure that anodal tDCS was having an effect on the visual  
53 cortex, fMRI measurements of visual cortex activation in response to counter-  
54 phasing checkerboard stimuli presented to either the amblyopic or non-  
55 amblyopic eye were made after real and sham anodal tDCS in a group of  
56 responders (n = 5). After sham tDCS there was a greater response  
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throughout the primary and extrastriate visual cortex when observers viewed with their fellow relative to their amblyopic eye. This reduction in the ability of the amblyopic eye to drive neural responses throughout the visual cortex has been reported in a number of previous fMRI studies (e.g.<sup>87</sup>) and may reflect a chronic suppression of information from the amblyopic eye. Notably, this response asymmetry between the two eyes was significantly reduced after real anodal tDCS suggesting that anodal tDCS acted to equate or “balance” the neural response to input for the two eyes possibly by reducing chronic suppression. This rebalancing was most pronounced within V2 and V3<sup>77</sup>. More work with larger numbers of patients and a variety of visual function measures will be required to assess the potential for the clinical use of brain stimulation techniques in amblyopia treatment. However the current data show that visual function can be improved, albeit transiently, after a brief intervention, possibly due to a reduction in the strength of suppressive interactions within the visual cortex.

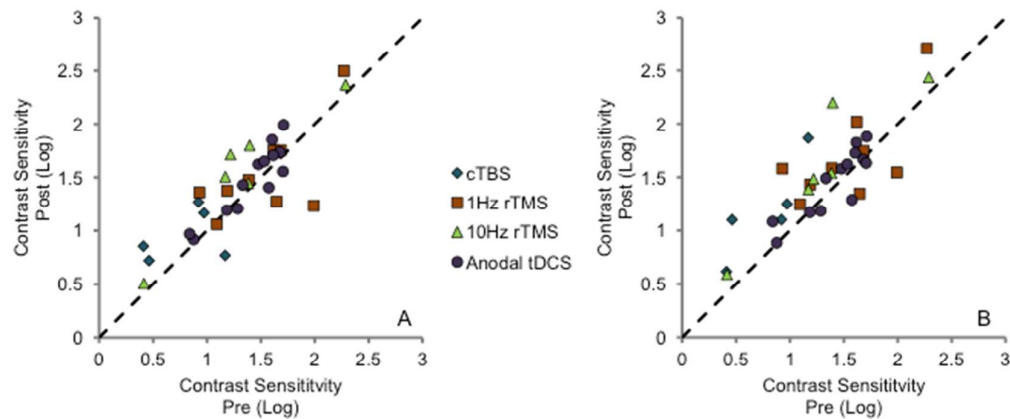


Figure 8. A comparison of log contrast sensitivity for a fixed high spatial frequency before, after (panel A) and 30 minutes after (panel B) different types of non-invasive stimulation of the visual cortex (continuous theta burst; cTBS, 1Hz and 10Hz repetitive transcranial magnetic stimulation; rTMS, and anodal transcranial direct current stimulation; tDCS). Data points above the unity lines indicate an improvement. N = 27 adults, participants with 10Hz rTMS data (n = 6) also took part in the 1Hz rTMS experiment. On average across all studies contrast sensitivity improved 0.09 log units directly after stimulation (95% CI 0.005 to 0.02) and 0.2 log units 30 minutes after stimulation (95% CI 0.1 to 0.3). Data replotted from<sup>77-79</sup>.

#### 4.2 Binocular treatment of amblyopia

A related approach to the treatment of amblyopia that is in a more advanced state of development involves dichoptic perceptual learning. The first version of this treatment was based on the dichoptic global motion task modified for the measurement of suppression that is described above (section 3.2). Knowing that binocular function was possible in adults with amblyopia when the contrast of the images shown to each eye was offset sufficiently in favor of the amblyopic eye, we wanted to know whether binocular combination could be strengthened. In our first experiment, ten adults with strabismic amblyopia practiced the dichoptic global motion task intensively over a period of several

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3 weeks<sup>34, 35</sup>. At the end of the study 6/9 participants no longer needed a  
4 contrast difference between the two eyes to allow for normal binocular  
5 combination of the signal and noise. Furthermore, visual acuity improved by  
6 an average of 0.26 LogMAR (95% CI 0.15 to 0.37 LogMAR, Figure 9  
7 diamonds) and 8/10 patients improved in stereopsis with 6 patients going from  
8 no measureable stereopsis on the RanDot test to stereopsis in the range of  
9 200-40 seconds of arc. These effects were striking as at no point during the  
10 study was the fellow eye patched. The transfer of the training effect from the  
11 dichoptic global motion task to improved monocular and binocular visual  
12 function in these adult patients suggested that suppression of the amblyopic  
13 eye may play a causal role in amblyopia and that reducing suppression  
14 enabled plasticity with the visual cortex.  
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18 In order to translate these results into a clinical context we incorporated the  
19 dichoptic contrast offset technique into a version of the videogame Tetris  
20 which requires players to tessellate falling blocks together. Some blocks are  
21 shown to the amblyopic eye at high contrast and others to the fellow eye at a  
22 low contrast tailored to each patient's level of suppression. Both eyes must be  
23 used simultaneously to play the game and successful game play results in a  
24 reduction of the contrast difference between the two eyes. This game has  
25 been deployed on a pair of video goggles with a separate screen for each eye  
26 and portable iPod Touch and iPad devices for which dichoptic viewing is  
27 enabled using either a lenticular overlay screen or red/green anaglyph  
28 glasses. To date there are 63 published cases of patients treated using the  
29 Tetris method with ages ranging from 5 to 51 years and treatment duration  
30 ranging from 5 hours to 40 hours<sup>88-93</sup>. Across studies the average  
31 improvement in amblyopic eye visual acuity was 0.21 LogMAR (95% CI 0.17  
32 to 0.25 LogMAR) and 42/63 patients (67%) of patients improved in stereopsis  
33 with 15/63 patients (24%) recovering stereo after treatment having no  
34 measureable stereo pre-treatment. Acuity and stereopsis improvements for all  
35 published cases treated with either the dot stimulus or the Tetris videogame  
36 are shown in Figure 9. A univariate ANOVA conducted on the change in  
37 LogMAR amblyopic eye acuity from pre to post treatment with factors of  
38 amblyopia type (anisometropic vs. strabismic vs. mixed), age and treatment  
39 duration in hours revealed no significant main effects or interactions. In  
40 addition, the proportion of patients who improved in stereopsis was similar  
41 across the amblyopia subtypes of anisometropic (10/32 improved, 31%),  
42 strabismic (7/19, 37%) and mixed (4/11, 36%). Therefore these initial data  
43 suggest that the effect of the treatment is independent of age and amblyopia  
44 subtype. Randomized clinical trials are currently underway to assess the  
45 efficacy of this treatment approach in larger groups of patients.  
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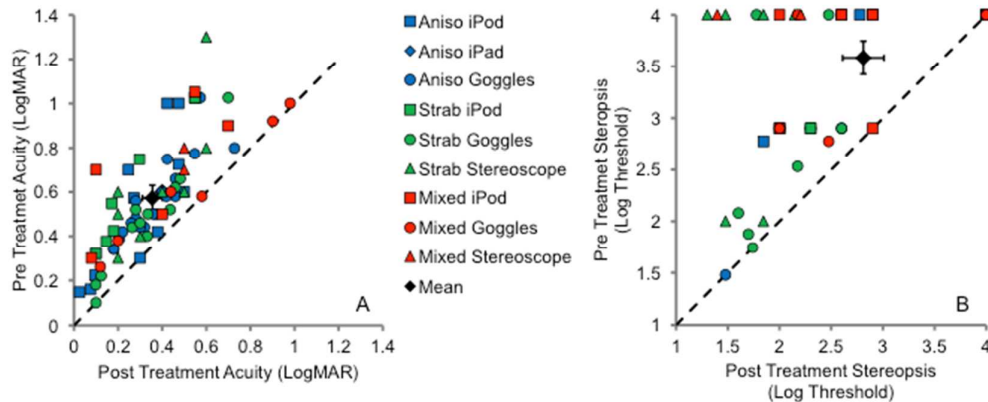


Figure 9. Improvements in amblyopic eye visual acuity (A) and stereopsis (B) for the 73 published cases of amblyopia treated using the dichoptic contrast balanced approach (either global motion or Tetris). Data points above the unity lines indicate improvements. Participants treated with the stereoscope viewed dichoptic global motion stimuli. All other participants played the modified Tetris game. Data are shown as log threshold for stereopsis and nil stereopsis results have been arbitrarily assigned a value of 4 for illustrative purposes. 20 patients had no measurable stereopsis both before and after treatment (data points overlap in to top right hand corner of panel B). Only visual acuity results were reported for the single case treated with an iPad device. Data are from <sup>35, 36, 58, 76, 88-90, 92</sup>.

Evidence to support the argument that the therapeutic effect of the dichoptic treatment is due to strengthening of binocular combination has recently been reported <sup>58</sup>. In this study, dichoptic treatment using the modified Tetris game was directly compared to monocular treatment whereby all the Tetris blocks were presented to the amblyopic eye at high contrast and the fellow eye was patched. The results were clear; dichoptic treatment was far superior to monocular treatment (Figure 10A and B) demonstrating that contrast balanced binocular stimulation underlies the treatment effect. Converging evidence has come from another recent study demonstrating that dichotic Tetris combined with anodal tDCS of primary visual cortex results in greater improvements in stereopsis than dichoptic Tetris alone <sup>76</sup> (Figure 10C). In other words; the combination of two interventions that reduce suppression within the visual cortex enhanced improvements in binocular visual function in adult amblyopes.

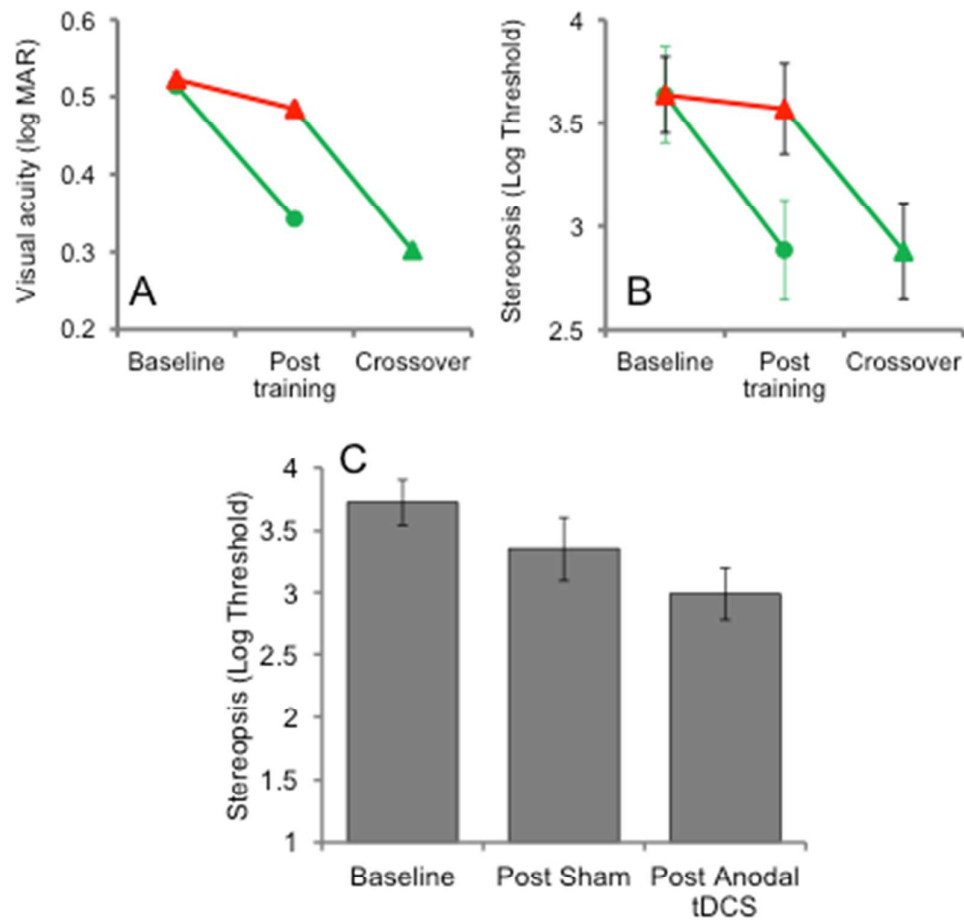


Figure 10. A direct comparison between two weeks of monocular Tetris play (red lines) and dichoptic Tetris treatment (green lines) in 18 adult amblyopes ( $n = 9$  adults per group, panels A and B). Dichoptic treatment resulted in far greater improvements in acuity (panel A) and stereopsis (panel B) than monocular treatment. Furthermore, participants in the monocular group exhibited substantial improvements when they were crossed over to binocular treatment (right most green lines). Panel C shows stereopsis at baseline and after sham or real anodal tDCS combined with binocular Tetris treatment ( $n = 16$  adults, randomized crossover design). The combined anodal tDCS and binocular Tetris treatment resulted in significantly greater improvements in stereopsis than combined sham tDCS and binocular treatment. Error bars show SEM, nil stereopsis results were allocated a log threshold of 4 for plotting. This substitution was not required for statistical significance. Data replotted from <sup>58, 76</sup>.

#### 4.3 Interim summary

Non-invasive brain stimulation techniques and dichoptic perceptual learning have been found to induce improvements in adults with amblyopia. These initial data indicate that suppressive interactions within the visual cortex are a viable target for amblyopia treatment and that suppression gates plasticity

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3 within the amblyopic visual cortex of adults. In particular, our novel dichoptic  
4 perceptual learning paradigm, in the form of a videogame, has the potential to  
5 revolutionize the treatment of amblyopia and provide a treatment option for  
6 adults not currently treated.  
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## 8 9 5. Conclusions

10  
11 A number of conclusions may be drawn from the evidence presented in the  
12 preceding sections. Firstly, visual function in the amblyopic eye is limited by  
13 the weak and noisy nature of inputs from this eye to the visual cortex as well  
14 as suppression of these inputs by information from the fellow eye, although  
15 there is still much to learn about the connection between these two  
16 phenomena. Crucially, when these impediments to visual function are  
17 accounted for, intact binocular mechanisms are revealed. Secondly, the  
18 strength of binocular combination (or the reciprocal; the strength of amblyopic  
19 eye suppression) can be objectively quantified using psychophysical tasks  
20 that target the primary visual cortex as well as dorsal or ventral extrastriate  
21 areas. The measurements reveal that stronger suppression is associated with  
22 poorer visual function in amblyopes and that suppression can be modulated in  
23 both amblyopes and observers with normal vision using partial occlusion  
24 techniques and, unexpectedly, short term occlusion of the weaker eye.  
25 Thirdly, dichoptic perceptual learning, designed to strengthen binocular  
26 combination by reducing suppression, improves both stereopsis and acuity in  
27 adults and children with amblyopia. These effects can be enhanced by non-  
28 invasive brain stimulation techniques which can also improve contrast  
29 sensitivity in their own right, possibly by reducing suppression of inputs from  
30 the amblyopic to the cortex. As a whole, these results lead us to question the  
31 prevalent view that amblyopia is primarily a disorder of monocular vision and  
32 should be treated accordingly with monocular occlusion. If we are open to the  
33 possibility that binocular interactions lie at the heart of amblyopia, then we  
34 could be at the threshold of a new age of therapeutic interventions that don't  
35 involve patching the fellow fixing eye.  
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41  
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## 47 48 7 References

- 49  
50  
51 1. Holmes JM, Clarke MP. Amblyopia. *Lancet*. 2006;367(9519):1343-51.  
52 Epub 2006/04/25.  
53 2. McKee SP, Levi DM, Movshon JA. The pattern of visual deficits in  
54 amblyopia. *Journal of vision*. 2003;3(5):380-405. Epub 2003/07/24.  
55 3. Campbell FW, Green DG. Monocular versus binocular visual acuity.  
56 *Nature*. 1965;208(5006):191-2. Epub 1965/10/09.  
57  
58  
59  
60

- 1
- 2
- 3 4. Meese TS, Georgeson MA, Baker DH. Binocular contrast vision at and
- 4 above threshold. *Journal of vision*. 2006;6(11), 1224-1243.
- 5 5. Lema SA, Blake R. Binocular summation in normal and stereoblind
- 6 humans. *Vision research*. 1977;17(6):691-5. Epub 1977/01/01.
- 7 6. Levi DM, Harwerth RS, Smith EL. Binocular interactions in normal and
- 8 anomalous binocular vision. *Documenta ophthalmologica Advances in*
- 9 *ophthalmology*. 1980;49(2):303-24. Epub 1980/10/15.
- 10 7. Pardhan S, Gilchrist J. Binocular contrast summation and inhibition in
- 11 amblyopia. The influence of the interocular difference on binocular contrast
- 12 sensitivity. *Documenta ophthalmologica Advances in ophthalmology*.
- 13 1992;82(3):239-48. Epub 1992/01/01.
- 14 8. Pardhan S, Whitaker A. Binocular summation in the fovea and
- 15 peripheral field of anisometropic amblyopes. *Current eye research*.
- 16 2000;20(1):35-44. Epub 1999/12/28.
- 17 9. Hubel DH, Wiesel TN. Binocular interaction in striate cortex of kittens
- 18 reared with artificial squint. *Journal of neurophysiology*. 1965;28(6):1041-59.
- 19 Epub 1965/11/01.
- 20 10. Baker DH, Meese TS, Mansouri B, Hess RF. Binocular summation of
- 21 contrast remains intact in strabismic amblyopia. *Investigative ophthalmology &*
- 22 *visual science*. 2007;48(11):5332-8. Epub 2007/10/27.
- 23 11. Harrad RA, Hess RF. Binocular integration of contrast information in
- 24 amblyopia. *Vision research*. 1992;32(11):2135-50. Epub 1992/11/01.
- 25 12. Baker DH, Meese TS, Hess RF. Contrast masking in strabismic
- 26 amblyopia: attenuation, noise, interocular suppression and binocular
- 27 summation. *Vision research*. 2008;48(15):1625-40. Epub 2008/06/13.
- 28 13. Bradley A, Ohzawa I. A comparison of contrast detection and
- 29 discrimination. *Vision research*. 1986;26(6):991-7. Epub 1986/01/01.
- 30 14. Hess RF, Bradley A, Piotrowski L. Contrast-coding in amblyopia. I.
- 31 Differences in the neural basis of human amblyopia. *Proc R Soc Lond B Biol*
- 32 *Sci*. 1983;217(1208):309-30. Epub 1983/02/22.
- 33 15. Foley JM. Human luminance pattern-vision mechanisms: masking
- 34 experiments require a new model. *Journal of the Optical Society of America*
- 35 *A, Optics, image science, and vision*. 1994;11(6):1710-9. Epub 1994/06/01.
- 36 16. Baker DH. What is the primary cause of individual differences in
- 37 contrast sensitivity? *PLOS One*. 2013; 8(7): e69536
- 38 17. Pelli DG, Farell B. Why use noise? *J Opt Soc Am A*. 1999;16(3):647-
- 39 53.
- 40 18. Huang C, Tao L, Zhou Y, Lu ZL. Treated amblyopes remain deficient in
- 41 spatial vision: a contrast sensitivity and external noise study. *Vision research*.
- 42 2007;47(1):22-34. Epub 2006/11/14.
- 43 19. Pelli DG, Levi DM, Chung STL. Using visual noise to characterize
- 44 amblyopic letter identification. *Journal of vision*. 2004;4(10).
- 45 20. Levi DM, Klein SA. Noise Provides Some New Signals About the
- 46 Spatial Vision of Amblyopes. *The Journal of Neuroscience*. 2003;23(7):2522-
- 47 6.
- 48 21. Levi DM, Klein SA, Chen I. The response of the amblyopic visual
- 49 system to noise. *Vision research*. 2007;47(19):2531-42. Epub 2007/08/19.
- 50 22. Levi DM, Klein SA, Chen I. What limits performance in the amblyopic
- 51 visual system: Seeing signals in noise with an amblyopic brain. *Journal of*
- 52 *vision*. 2008;8(4).
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

23. Hess RF, Field DJ. Is the spatial deficit in strabismic amblyopia due to loss of cells or an uncalibrated disarray of cells? *Vision research*. 1994;34(24):3397-406.
24. Ding J, Sperling G. A gain-control theory of binocular combination. *Proceedings of the National Academy of Sciences of the United States of America*. 2006;103(4):1141-6. Epub 2006/01/18.
25. Ding J, Klein SA, Levi DM. Binocular combination in abnormal binocular vision. *Journal of vision*. 2013;13(2):14. Epub 2013/02/12.
26. Huang C, Zhou J, Lu Z, Zhou Y. Deficient binocular combination reveals mechanisms of anisometropic amblyopia: Signal attenuation and interocular inhibition. *Journal of vision*. 2011;11(6):1-17.
27. Huang CB, Zhou J, Lu ZL, Feng L, Zhou Y. Binocular combination in anisometropic amblyopia. *Journal of vision*. 2009;9(3):17 1-6. Epub 2009/09/18.
28. Travers T. Suppression of vision in squint and its association with retinal correspondence and amblyopia. *British J Ophthalmology*. 1938;22:577-604.
29. Pratt-Johnson JA, Wee HS, Ellis S. Suppression associated with esotropia. *Can J Ophthalmol*. 1967;2(4):284-91. Epub 1967/10/01.
30. Jampolsky A. Characteristics of suppression in strabismus. *AMA Arch Ophthalmol*. 1955;54(5):683-96. Epub 1955/11/01.
31. Joosse MV, Simonsz HJ, Spekreijse H, Mulder PG, van Minderhout HM. The optimal stimulus to elicit suppression in small-angle convergent strabismus. *Strabismus*. 2000;8(4):233-42. Epub 2001/03/23.
32. Joosse MV, Simonsz HJ, van Minderhout EM, Mulder PG, de Jong PT. Quantitative visual fields under binocular viewing conditions in primary and consecutive divergent strabismus. *Graefes Arch Clin Exp Ophthalmol*. 1999;237(7):535-45. Epub 1999/07/29.
33. Joosse MV, Simonsz HJ, van Minderhout HM, de Jong PT, Noordzij B, Mulder PG. Quantitative perimetry under binocular viewing conditions in microstrabismus. *Vision research*. 1997;37(19):2801-12. Epub 1997/11/28.
34. Hess RF, Mansouri B, Thompson B. A new binocular approach to the treatment of Amblyopia in adults well beyond the critical period of visual development. *Restorative Neurology and Neuroscience*. 2010;28:1-10.
35. Hess RF, Mansouri B, Thompson B. A binocular approach to treating amblyopia: antisuppression therapy. *Optom Vis Sci*. 2010;87(9):697-704. Epub 2010/07/14.
36. Hess RF, Mansouri B, Thompson B. Restoration of binocular vision in amblyopia. *Strabismus*. 2011;19(3):110-8. Epub 2011/08/30.
37. Mansouri B, Thompson B, Hess RF. Measurement of suprathreshold binocular interactions in amblyopia. *Vision research*. 2008;48(28):2775-84. Epub 2008/09/24.
38. Li J, Lam CS, Yu M, Hess RF, Chan LY, Maehara G, et al. Quantifying sensory eye dominance in the normal visual system: a new technique and insights into variation across traditional tests. *Investigative ophthalmology & visual science*. 2010;51(12):6875-81. Epub 2010/07/09.
39. Black J, Maehara G, Thompson B, Hess RF. A compact clinical instrument for quantifying suppression. *Optometry and Vision Science*. 2011;88(2):334-42.

- 1
- 2
- 3 40. Li J, Hess RF, Chan LY, Deng D, Chen X, Yu M, et al. How Best to
- 4 Assess Suppression in Patients with High Anisometropia. *Optom Vis Sci.*
- 5 2013;in press. Epub 2013/01/08.
- 6
- 7 41. Husk JS, Huang P-C, Hess RF. Orientation coherence sensitivity. *J of*
- 8 *Vision.* 2012;12(6):doi: 10.1167/12.6.18. Print 2012.
- 9
- 10 42. Zhou J, Huang PC, Hess RF. Interocular suppression in amblyopia for
- 11 global orientation processing. *Journal of vision.* 2013;13(5):19. Epub
- 12 2013/04/24.
- 13
- 14 43. Holopigian K, Blake R, Greenwald MJ. Clinical suppression and
- 15 amblyopia. *Investigative ophthalmology & visual science.* 1988;29(3):444-51.
- 16
- 17 44. Goodman LK, Black JM, Phillips G, Hess RF, Thompson B. Excitatory
- 18 binocular interactions in two cases of alternating strabismus. *Journal of*
- 19 *AAPOS : the official publication of the American Association for Pediatric*
- 20 *Ophthalmology and Strabismus / American Association for Pediatric*
- 21 *Ophthalmology and Strabismus.* 2011;15(4):345-9. Epub 2011/09/13.
- 22
- 23 45. Li J, Thompson B, Lam CSY, Deng D, Chan LYL, Maehara G, et al.
- 24 The role of suppression in amblyopia. *Invest Ophthal Vis Sci.*
- 25 2011;52(7):4167-76.
- 26
- 27 46. Li J, Hess RF, Chan LYL, Deng D, Yang X, Chen X, et al. Quantitative
- 28 Measurement of Interocular Suppression in Anisometric Amblyopia: A
- 29 Case-Control Study. *Ophthalmology.* 2013;120(8):1672-80.
- 30
- 31 47. Narasimhan S, Harrison ER, Giaschi DE. Quantitative measurement of
- 32 interocular suppression in children with amblyopia. *Vision research.*
- 33 2012;66:1-10.
- 34
- 35 48. Pratt-Johnson JA, Tillson G, Pop A. Suppression in strabismus and the
- 36 hemiretinal trigger mechanism. *Arch Ophthalmol.* 1983;101(2):218-24. Epub
- 37 1983/02/01.
- 38
- 39 49. Babu RJ, Clavagnier SR, Bobier W, Thompson B, F. HR. The regional
- 40 extent of suppression:strabismics vs non-strabismics. *IOVS.* 2013;in press.
- 41
- 42 50. Lunghi C, Burr DC, Morrone C. Brief periods of monocular deprivation
- 43 disrupt ocular balance in human adult visual cortex. *Curr Biol.*
- 44 2012;21(14):R538-9. Epub 2011/07/26.
- 45
- 46 51. Zhou J, Clavagnier S, Hess RF. Short-term monocular deprivation
- 47 strengthen the patched eye's contribution to binocular combination. *J Vision.*
- 48 2013;(in submission).
- 49
- 50 52. Zhang P, Bobier W, Thompson B, Hess RF. Binocular balance in
- 51 normal vision and its modulation by mean luminance. *Optom Vis Sci.*
- 52 2011;88(9):1072-9. Epub 2011/06/07.
- 53
- 54 53. Li J, Thompson B, Ding Z, Chan LY, Chen X, Yu M, et al. Does partial
- 55 occlusion promote normal binocular function? *Investigative ophthalmology &*
- 56 *visual science.* 2012;53(11):6818-27. Epub 2012/09/08.
- 57
- 58 54. Zhou J, Jia W, Huang CB, Hess RF. The Effect of Unilateral Mean
- 59 Luminance on Binocular Combination in normal and amblyopic vision. *Sci*
- 60 *Rep.* 2013;3:2012. Epub 2013/06/19.
- 55 55. Bi H, Zhang B, Tao X, Harwerth RS, Smith EL, 3rd, Chino YM.
- 56 Neuronal responses in visual area V2 (V2) of macaque monkeys with
- 57 strabismic amblyopia. *Cereb Cortex.* 2011;21(9):2033-45. Epub 2011/01/26.
- 58
- 59 56. Sengpiel F, Jirjann KU, Vorobyov V, Eysel UT. Strabismic
- 60 suppression is mediated by inhibitory interactions in the primary visual cortex. *Cereb Cortex.* 2006;16(12):1750-8.

- 1
- 2
- 3 57. Hess RF, Mansouri B, Thompson B, Gheorghiu E. Latent stereopsis for
- 4 motion in depth in strabismic amblyopia. *Investigative ophthalmology & visual*
- 5 *science*. 2009;50(10):5006-16. Epub 2009/05/22.
- 6
- 7 58. Li J, Thompson B, Deng D, Chan L, Yu M, Hess RF. Dichoptic training
- 8 enables the adult amblyopic brain to learn. *Current Biology*. 2013:In Press.
- 9
- 10 59. Hess RF, Thompson B. New insights into amblyopia: Binocular therapy
- 11 and noninvasive brain stimulation. *Journal of American Association for*
- 12 *Pediatric Ophthalmology and Strabismus*. 2013;17(1):89-93.
- 13
- 14 60. Wagner T, Valero-Cabre A, Pascual-Leone A. Noninvasive human
- 15 brain stimulation. *Annual review of biomedical engineering*. 2007;9:527-65.
- 16 Epub 2007/04/21.
- 17
- 18 61. George MS, Padberg F, Schlaepfer TE, O'Reardon JP, Fitzgerald PB,
- 19 Nahas ZH, et al. Controversy: Repetitive transcranial magnetic stimulation or
- 20 transcranial direct current stimulation shows efficacy in treating psychiatric
- 21 diseases (depression, mania, schizophrenia, obsessive-compulsive disorder,
- 22 panic, posttraumatic stress disorder). *Brain Stimulation*. 2009;2(1):14-21.
- 23
- 24 62. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy
- 25 to improve neurorehabilitation after stroke? *Lancet neurology*. 2006;5(8):708-
- 26 12. Epub 2006/07/22.
- 27
- 28 63. Vanneste S, Langguth B, De Ridder D. Do tDCS and TMS influence
- 29 tinnitus transiently via a direct cortical and indirect somatosensory modulating
- 30 effect? A combined TMS-tDCS and TENS study. *Brain Stimulation*.
- 31 2011;4(4):242-52.
- 32
- 33 64. Fregni F, Boggio PS, Santos MC, Lima M, Vieira AL, Rigonatti SP, et
- 34 al. Noninvasive cortical stimulation with transcranial direct current stimulation
- 35 in Parkinson's disease. *Movement disorders : official journal of the Movement*
- 36 *Disorder Society*. 2006;21(10):1693-702. Epub 2006/07/04.
- 37
- 38 65. Fregni F, Freedman S, Pascual-Leone A. Recent advances in the
- 39 treatment of chronic pain with non-invasive brain stimulation techniques.
- 40 *Lancet neurology*. 2007;6(2):188-91. Epub 2007/01/24.
- 41
- 42 66. Hallett M. Transcranial magnetic stimulation: a primer. *Neuron*.
- 43 2007;55(2):187-99. Epub 2007/07/21.
- 44
- 45 67. Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of
- 46 the effects of rTMS on motor cortical excitability and inhibition. *Clinical*
- 47 *neurophysiology : official journal of the International Federation of Clinical*
- 48 *Neurophysiology*. 2006;117(12):2584-96. Epub 2006/08/08.
- 49
- 50 68. Huang YZ, Rothwell JC. The effect of short-duration bursts of high-
- 51 frequency, low-intensity transcranial magnetic stimulation on the human motor
- 52 cortex. *Clinical neurophysiology : official journal of the International*
- 53 *Federation of Clinical Neurophysiology*. 2004;115(5):1069-75. Epub
- 54 2004/04/07.
- 55
- 56 69. Nitsche MA, Paulus W. Excitability changes induced in the human
- 57 motor cortex by weak transcranial direct current stimulation. *The Journal of*
- 58 *physiology*. 2000;527 Pt 3:633-9. Epub 2000/09/16.
- 59
- 60 70. Antal A, Kincses TZ, Nitsche MA, Paulus W. Manipulation of
- phosphene thresholds by transcranial direct current stimulation in man.
- Experimental brain research Experimentelle Hirnforschung Experimentation*
- cerebrale*. 2003;150(3):375-8. Epub 2003/04/17.
71. Thompson B, Aaen-Stockdale C, Koski L, Hess RF. A double
- dissociation between striate and extrastriate visual cortex for pattern motion

- 1  
2  
3 perception revealed using rTMS. Human brain mapping. 2009;30(10):3115-  
4 26. Epub 2009/02/19.
- 5 72. Franca M, Koch G, Mochizuki H, Huang YZ, Rothwell JC. Effects of  
6 theta burst stimulation protocols on phosphene threshold. Clinical  
7 neurophysiology : official journal of the International Federation of Clinical  
8 Neurophysiology. 2006;117(8):1808-13. Epub 2006/06/27.
- 9 73. Thut G, Theoret H, Pfennig A, Ives J, Kampmann F, Northoff G, et al.  
10 Differential effects of low-frequency rTMS at the occipital pole on visual-  
11 induced alpha desynchronization and visual-evoked potentials. NeuroImage.  
12 2003;18(2):334-47. Epub 2003/02/22.
- 13 74. Accornero N, Li Voti P, La Riccia M, Gregori B. Visual evoked  
14 potentials modulation during direct current cortical polarization. Experimental  
15 brain research Experimentelle Hirnforschung Experimentation cerebrale.  
16 2007;178(2):261-6. Epub 2006/10/20.
- 17 75. Waterston ML, Pack CC. Improved discrimination of visual stimuli  
18 following repetitive transcranial magnetic stimulation. PLOS One.  
19 2010;5(4):e10354. Epub 2010/05/06.
- 20 76. Spiegel DP, Li J, Hess RF, Byblow WD, Deng D, Yu M, et al.  
21 Transcranial Direct Current Stimulation Enhances Recovery of Stereopsis in  
22 Adults With Amblyopia. Neurotherapeutics : the journal of the American  
23 Society for Experimental NeuroTherapeutics. 2013. Epub 2013/07/17.
- 24 77. Spiegel DP, Byblow WD, Hess RF, Thompson B. Anodal Transcranial  
25 Direct Current Stimulation Transiently Improves Contrast Sensitivity and  
26 Normalizes Visual Cortex Activation in Individuals With Amblyopia.  
27 Neurorehabilitation and neural repair. 2013. Epub 2013/06/19.
- 28 78. Clavagner S, Thompson B, Hess RF. Long Lasting Effects of Daily  
29 Theta Burst rTMS Sessions in the Human Amblyopic Cortex. Brain Stimul.  
30 2013. Epub 2013/05/15.
- 31 79. Thompson B, Mansouri B, Koski L, Hess RF. Brain plasticity in the  
32 adult: modulation of function in amblyopia with rTMS. Curr Biol.  
33 2008;18(14):1067-71. Epub 2008/07/19.
- 34 80. Talelli P, Greenwood RJ, Rothwell JC. Exploring Theta Burst  
35 Stimulation as an intervention to improve motor recovery in chronic stroke.  
36 Clinical neurophysiology : official journal of the International Federation of  
37 Clinical Neurophysiology. 2007;118(2):333-42. Epub 2006/12/15.
- 38 81. Silvanto J, Muggleton N, Walsh V. State-dependency in brain  
39 stimulation studies of perception and cognition. Trends in cognitive sciences.  
40 2008;12(12):447-54. Epub 2008/10/28.
- 41 82. Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, et al.  
42 Preconditioning of low-frequency repetitive transcranial magnetic stimulation  
43 with transcranial direct current stimulation: evidence for homeostatic plasticity  
44 in the human motor cortex. The Journal of neuroscience : the official journal of  
45 the Society for Neuroscience. 2004;24(13):3379-85. Epub 2004/04/02.
- 46 83. Bavelier D, Levi DM, Li RW, Dan Y, Hensch TK. Removing brakes on  
47 adult brain plasticity: from molecular to behavioral interventions. The Journal  
48 of neuroscience : the official journal of the Society for Neuroscience.  
49 2010;30(45):14964-71. Epub 2010/11/12.
- 50 84. Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses  
51 ZT, et al. Polarity-sensitive modulation of cortical neurotransmitters by  
52  
53  
54  
55  
56  
57  
58  
59  
60

- transcranial stimulation. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2009;29(16):5202-6. Epub 2009/04/24.
85. Spiegel DP, Hansen BC, Byblow WD, Thompson B. Anodal transcranial direct current stimulation reduces psychophysically measured surround suppression in the human visual cortex. *PLOS One*. 2012;7(5):e36220. Epub 2012/05/09.
86. Vanneste S, Focquaert F, Van de Heyning P, De Ridder D. Different resting state brain activity and functional connectivity in patients who respond and not respond to bifrontal tDCS for tinnitus suppression. *Experimental brain research Experimentelle Hirnforschung Experimentation cerebrale*. 2011;210(2):217-27. Epub 2011/03/26.
87. Barnes GR, Hess RF, Dumoulin SO, Achtman RL, Pike GB. The cortical deficit in humans with strabismic amblyopia. *The Journal of physiology*. 2001;533(Pt 1):281-97. Epub 2001/05/15.
88. Birch EE. Amblyopia and binocular vision. *Progress in retinal and eye research*. 2013;33:67-84. Epub 2012/12/04.
89. Spiegel DP. *Transcranial Direct Current Stimulation of the Healthy and Amblyopic Visual Cortex: Mechanisms and Action*. Auckland: University of Auckland 2013.
90. Black JM, Hess RF, Cooperstock JR, To L, Thompson B. The measurement and treatment of suppression in amblyopia. *Journal of visualized experiments : JoVE*. 2012(70):e3927. Epub 2012/12/29.
91. Hess RF, Thompson B, Black JM, Maehara G, Zhang P, Bobier WR, et al. An iPod treatment for Amblyopia: an Updated Binocular Approach. *Optometry*. 2012;83(2):87-94.
92. Knox PJ, Simmers AJ, Gray LS, Cleary M. An exploratory study: prolonged periods of binocular stimulation can provide an effective treatment for childhood amblyopia. *Investigative ophthalmology & visual science*. 2011;53(2):817-24. Epub 2011/12/16.
93. To L, Thompson B, Blum JR, Maehara G, Hess RF, Cooperstock JR. A game platform for treatment of amblyopia. *IEEE Trans Neural Syst Rehabil Eng*. 2011;19(3):280-9. Epub 2011/02/22.