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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 eye¹. However, amblyopia is characterized by a range of visual deficits that affect both monocular and binocular visual function². 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^{3,4}. 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 reduced⁵⁻⁸. Many researchers concluded from this that binocular combination simply did not occur in amblyopes, consistent with early physiological work on cats with surgically induced strabismus⁹. 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.¹⁰, 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 work⁶ 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 Hess¹¹ repeated the experiment on a larger number of amblyopes with varying aetiologies. Some of their results resembled those of

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3 the previous study⁶, 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 study¹² 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.
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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 Ohzawa¹³ 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 frequencies¹⁴).
20 This intriguing finding (since confirmed¹²) 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, see¹⁵), a vertical shift is produced only by changing the signal
25 to noise ratio¹⁶. If noise is increased in the amblyopic eye, this could be
26 assessed directly using the noise masking paradigm (e.g.¹⁷). 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 thresholds¹⁷. 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 study¹⁸ 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 evident¹⁹.
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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 eye²⁰⁻²² though it is unclear whether this is additive,
47 multiplicative or both^{12, 21}. 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 reported²³, 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 task¹²⁻¹⁴, 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 Sperling²⁴ to investigate amblyopia²⁵⁻²⁷. 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 threshold¹⁰.
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.¹² took a model developed to explain normal binocular
26 combination⁴ 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.^{26, 27} made similar modifications to the binocular model of Ding
44 and Sperling²⁴ 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.²⁵ 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 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 Travers²⁸ in Melbourne, Pratt-johnson²⁹ in the UK
21 and Jampolski³⁰ 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 it³¹⁻³³ 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 therapy³⁴⁻³⁶. 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 eye³⁷. 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 balanced³⁸. 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 version³⁷ 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 eye³⁹. 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 segregation⁴⁰.

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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 coherence⁴¹ that has been adapted⁴² 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° 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^{24, 26}.

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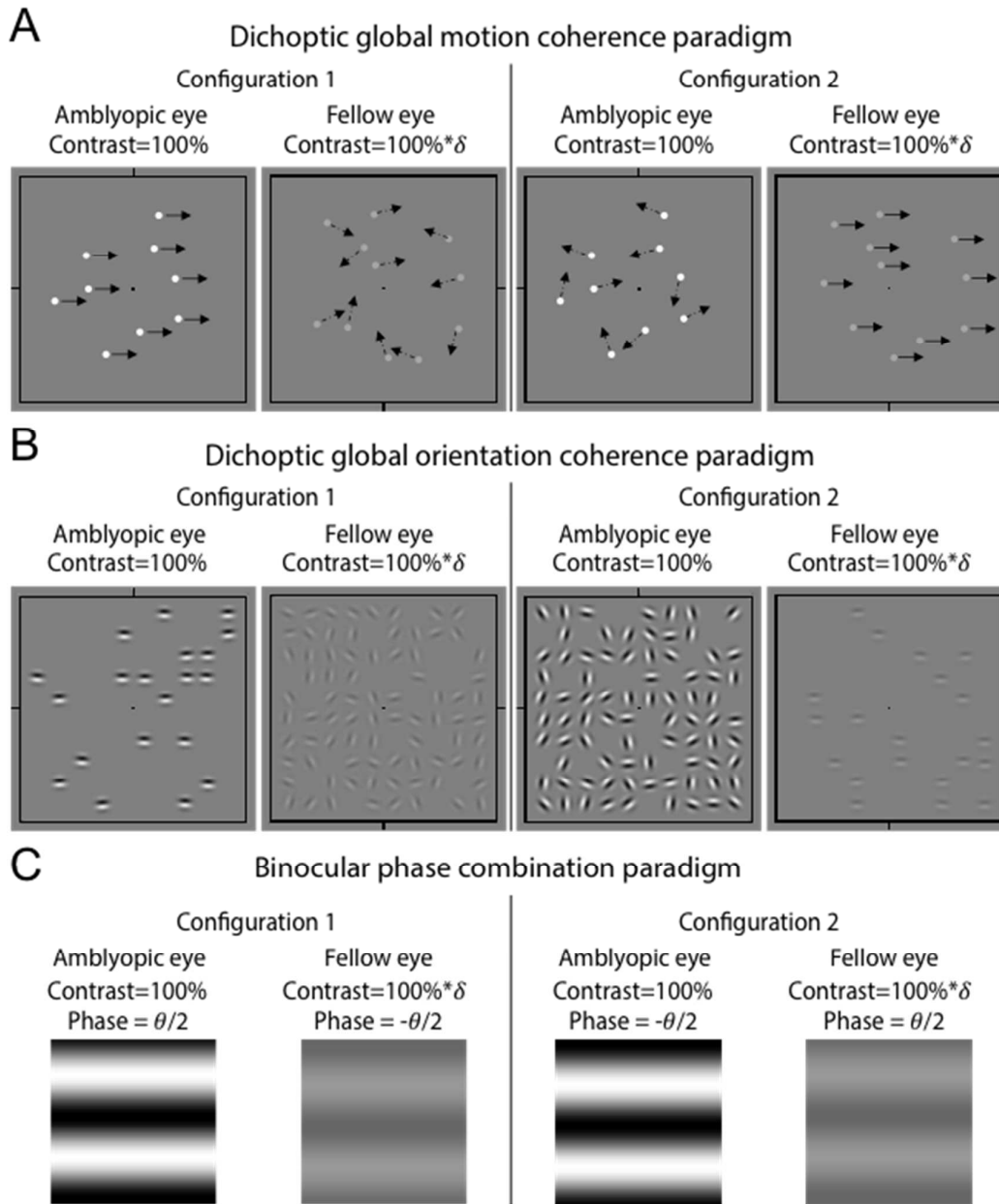


Figure 1. An illustration of the stimuli and paradigms used to measure interocular suppression. (A) The dichoptic global motion coherence paradigm. (B) The dichoptic global orientation coherence paradigm. (C) The binocular phase combination paradigm. See sections 3.1.1 to 3.1.3 for further details.

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 work⁴³ which involved 9 patients of whom 1/3 were alternating strabismics. Alternating strabismics typically have suppression (which may be very strong⁴⁴) 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 al⁴⁵ 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^{42, 46, 47}.

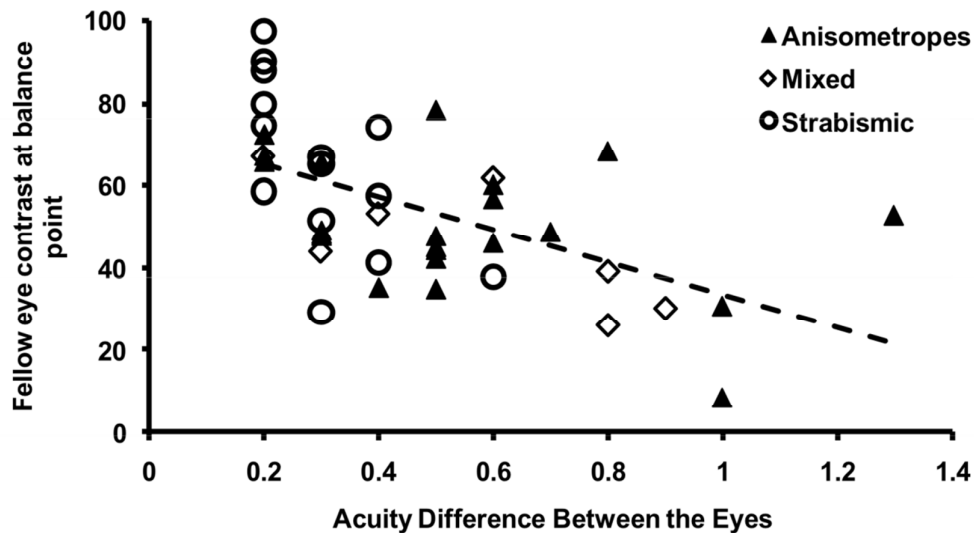


Figure 2. Mean fellow eye contrast at balance point as a function of interocular acuity difference (Log MAR) for 43 patients with amblyopia. Lower values on the Y axis indicate stronger suppression (see section 3.2 for details). There was a significant negative correlation ($p < 0.001$) indicating that stronger suppression was associated with greater acuity loss in the amblyopic eye. Figure reproduced from⁴⁵.

3.3. The regional distribution of suppression

Since the work of Travers²⁸, Jampolski³⁰ and Pratt-Johnson^{29, 48}, 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 means⁴⁹ 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.

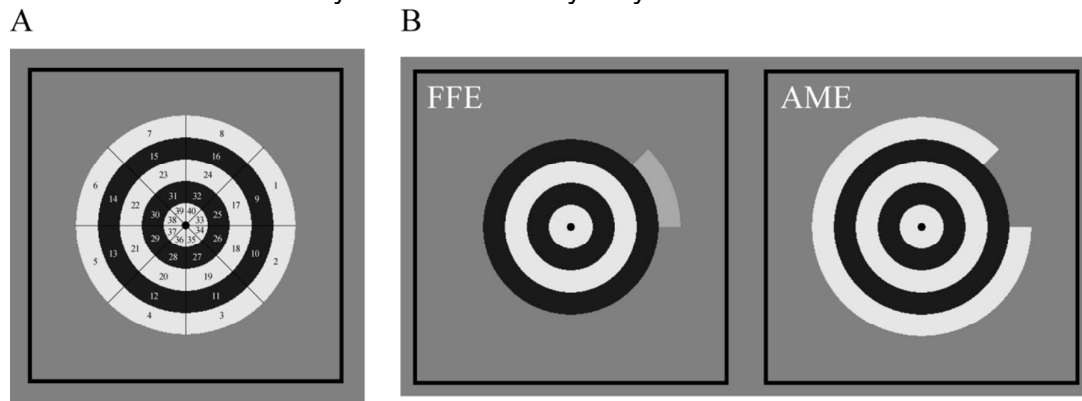


Figure 3. The annular-based suppression mapping stimulus. Panel A depicts the 40 regions of the visual field that were tested. The radius of the most eccentric ring is 10°. Panel B depicts the dichoptic testing arrangement. One segment was shown to the fellow eye and the remaining segments from the same 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 from⁴⁹.

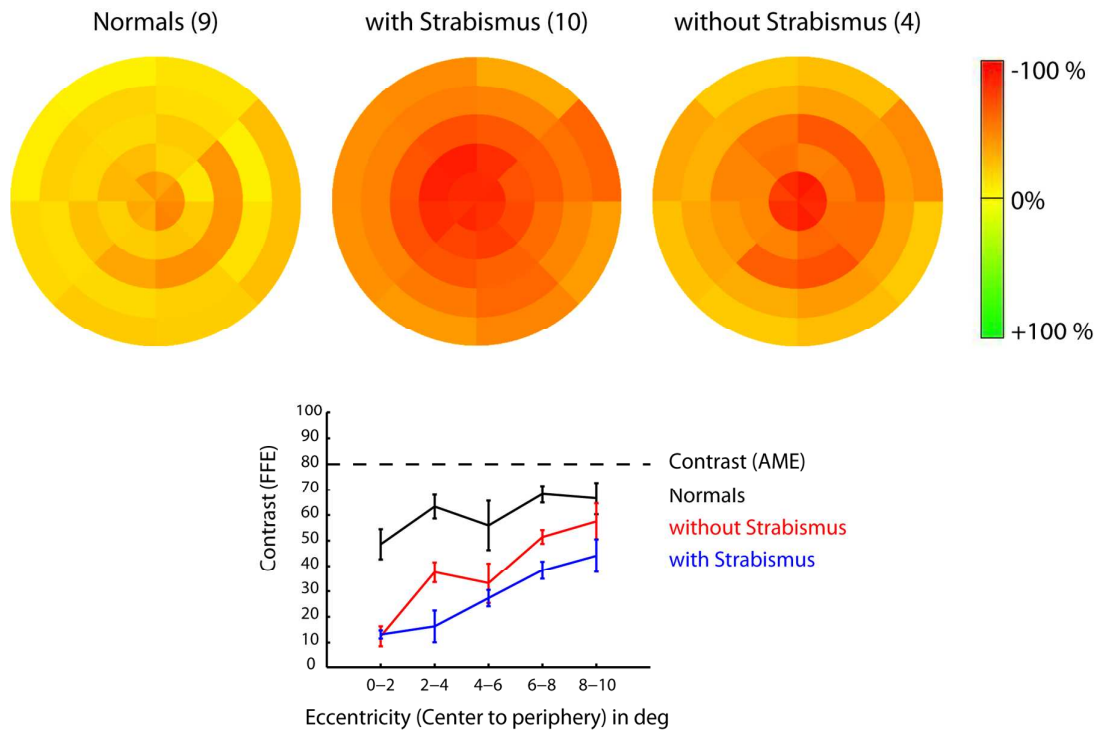


Figure 4. Average suppression maps for observers with normal binocular vision ($n = 10$) and amblyopes with ($n = 10$) and without ($n = 4$) strabismus. Amblyopia is associated with significantly stronger suppression than that found in normals. The color maps indicate the magnitude and extent of suppression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

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 rivalry⁵⁰ whereby the image shown to the previously patched eye becomes dominant. We investigated this effect further⁵¹ using the motion coherence test³⁷, the phase test²⁶ and the dichoptic contrast test²⁶ and found good support for this novel phenomenon. Examples of the results for the phase and motion coherence tests are shown in Figure 5.

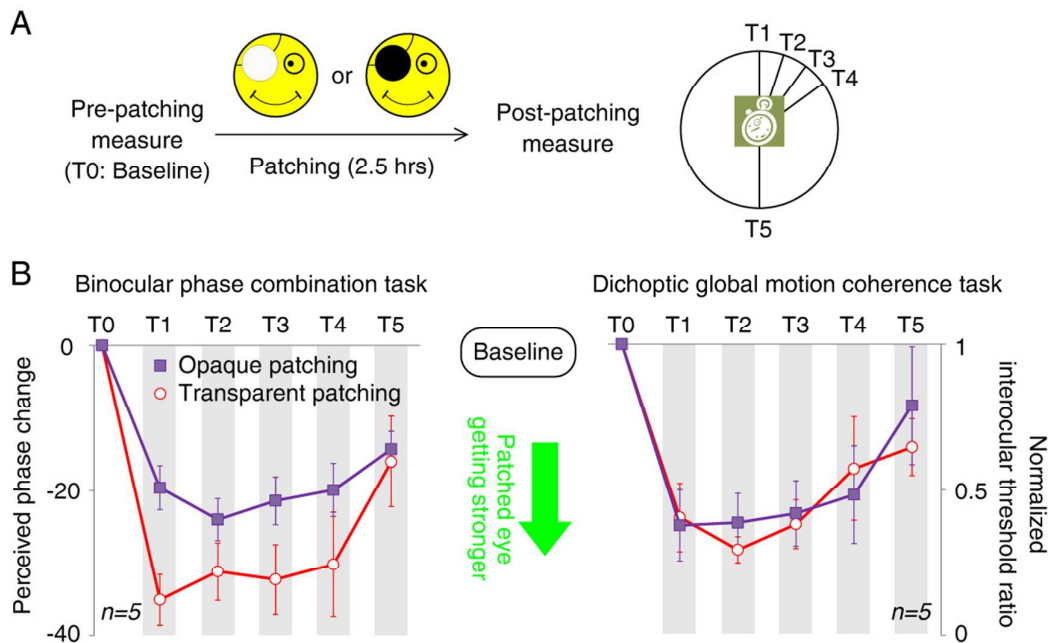


Figure 5. The effect of 2.5 hrs of monocular occlusion with either a light-tight patch or a diffuser on the binocular phase combination task and the dichoptic global motion coherence task. (A) Experimental protocol, (B) Patching effects on the binocular phase combination task (left panel) and dichoptic global motion coherence task (right panel). Error bars represent standard errors. Figure from⁵¹.

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) effect⁵¹.

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.

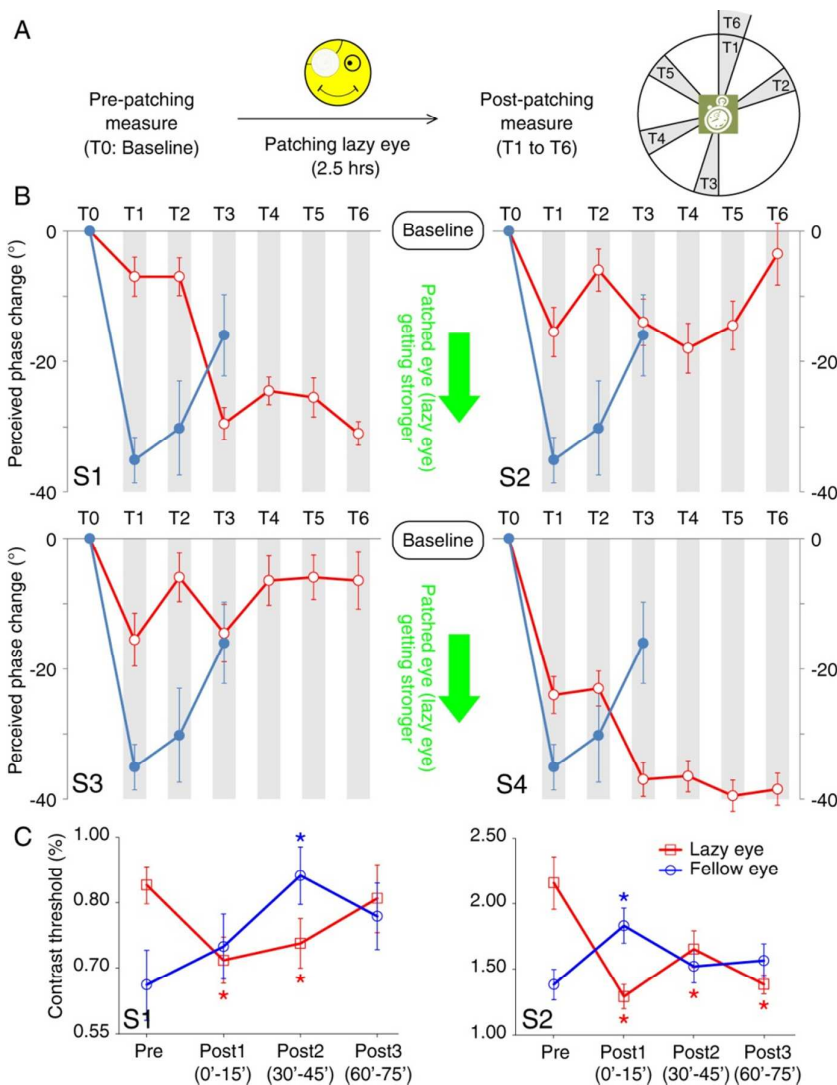


Figure 6. a) The time line of the patching and testing protocol. b) Measurement of binocular balance using the phase test after patching of the amblyopic eye for each of 4 observers with amblyopia (S1-S4). The red lines with open dots in each panel represent the time course of the perceived phase change 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 vision⁵².

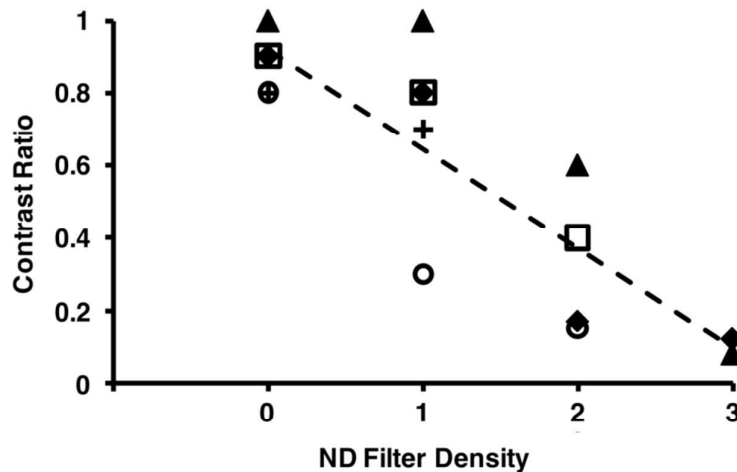


Figure 7. The contrast ratio between the eyes on the dichoptic global motion coherence task as a function of the strength of neutral density filter placed over the non-dominant eye for observers with normal binocular vision. A ratio of 1 on the Y-axis indicates normal binocular combination. Lower ratios 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. From⁵².

Figure 7 shows measurements of binocular balance in terms of the contrast ratio for the signal and noise within the dichoptic motion coherence task³⁷. 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 effects⁵³. 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^{53, 54}. 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 function⁵³. 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 processing⁵³. 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)⁵³.

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^{40, 45-47} and
49 compelling links between suppression and visual dysfunction have been
50 found in animal models of amblyopia and strabismus^{55, 56}. Initial evidence
51 also indicates that stronger suppression is associated with a poorer response
52 to occlusion therapy in children⁴⁷, even when factors such as pre-treatment
53 visual acuity and stereopsis are accounted for⁴⁶. This raises the possibility
54 that suppression not only masks latent visual capabilities⁵⁷ but also gates
55 visual cortex plasticity⁵⁸. 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 ⁵⁹ for a recent discussion of the issues involved).
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7 8 4.1 Non-invasive brain stimulation and amblyopia

9
10 Non-invasive brain stimulation techniques can be used to modulate
11 fundamental properties of neural systems such as excitation and inhibition ⁶⁰.
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 ⁶¹⁻
17 ⁶⁵. 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 ^{16, 66}. 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 ⁶⁷) or a series of "bursts" (e.g. theta burst
24 stimulation or TBS ⁶⁸), 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 ⁶⁹. 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) ⁷⁰⁻⁷⁵.
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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 ⁷⁶⁻
41 ⁷⁹. 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 ^{62, 80}. 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 ⁸¹. In particular,
49 brain stimulation may act to restore homeostasis to neural populations ⁸². 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 ⁶⁷ which has been strongly implicated as a "break" on
56 visual cortex plasticity in animal models of amblyopia ⁸³. Finally, anodal tDCS
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3 in particular has been shown to reduce GABA levels within the human motor
4 cortex⁸⁴ and behavioral evidence suggests that similar effects may occur
5 within the human visual cortex⁸⁵. 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 cortex⁵⁶. 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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12 Current evidence is generally consistent with this hypothesis (Figure 8).
13 Specifically, we have shown that non-invasive brain stimulation can improve
14 contrast sensitivity in at least a subset of adults with amblyopia. In the first
15 study to address this question we measured contrast sensitivity for low and
16 high spatial frequency Gabor targets (the exact spatial frequency was tailored
17 for each patient) before and after an inhibitory rTMS protocol (1Hz stimulation,
18 n = 9 patients) and an excitatory protocol (10Hz stimulation, n = 6 patients)
19 delivered to the primary visual cortex⁷⁹. Stimulation of the motor cortex was
20 used as a control condition. Both types of rTMS resulted in significant
21 improvements in contrast sensitivity (a mean improvement of approximately
22 40%) when high spatial frequency targets were viewed by the amblyopic eye
23 (7/9 patients improved for 1Hz and 6/6 for 10 Hz, including the two patients
24 who did not improve for 1Hz). No improvements were found for the low spatial
25 frequency target for which the amblyopic eyes did not show a pronounced
26 contrast sensitivity deficit at baseline. Furthermore, improvements were not
27 found for the fellow eye after visual cortex stimulation or for either eye after
28 motor cortex stimulation, indicating that the rTMS effects specifically targeted
29 amblyopic eye function. The improvements were transient however, with
30 thresholds returning to baseline within approximately 24 hours after
31 stimulation. In a follow-up study we investigated the effect of repeated
32 administration of rTMS (in this case continuous TBS; cTBS) over five
33 consecutive days in four adults with amblyopia⁷⁸. The acute effects of a single
34 stimulation session (measured in 5 patients) resulted in improvements in
35 contrast sensitivity for the amblyopic eye of a similar magnitude to the original
36 study. Furthermore there was a cumulative effect of cTBS on contrast
37 sensitivity over the first two sessions which stabilized over subsequent
38 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)⁷⁷. 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-responders⁸⁶
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.⁸⁷) 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 V3⁷⁷. 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.

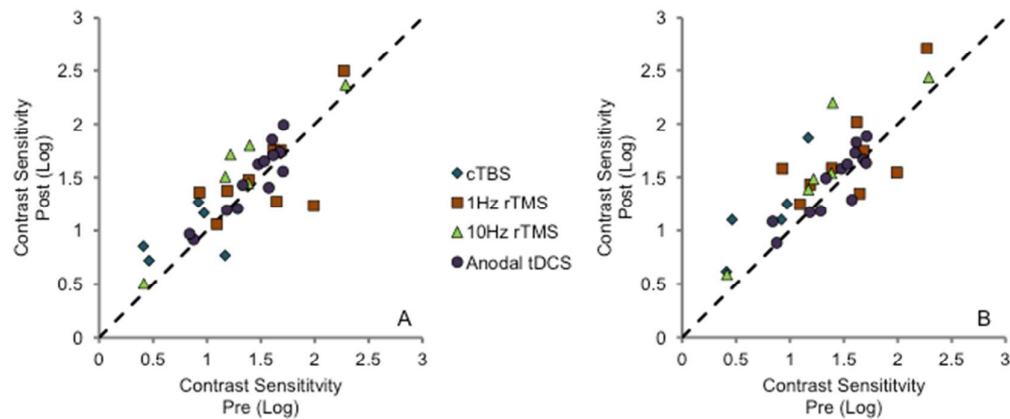


Figure 8. A comparison of log contrast sensitivity for a fixed high spatial frequency before, after (panel A) and 30 minutes after (panel B) different types of non-invasive stimulation of the visual cortex (continuous theta burst; cTBS, 1Hz and 10Hz repetitive transcranial magnetic stimulation; rTMS, 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 from⁷⁷⁻⁷⁹.

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^{34, 35}. 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 hours⁸⁸⁻⁹³. 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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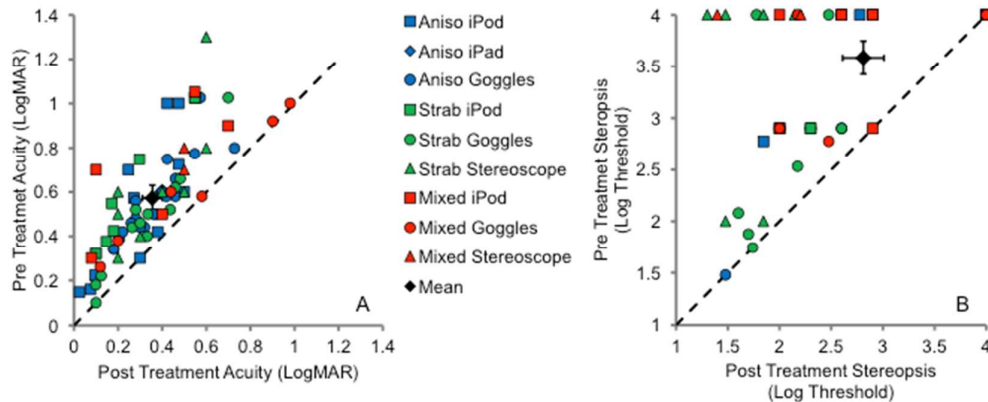


Figure 9. Improvements in amblyopic eye visual acuity (A) and stereopsis (B) for the 73 published cases of amblyopia treated using the dichoptic contrast balanced approach (either global motion or Tetris). Data points above the unity lines indicate improvements. Participants treated with the stereoscope 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 ^{35, 36, 58, 76, 88-90, 92}.

Evidence to support the argument that the therapeutic effect of the dichoptic treatment is due to strengthening of binocular combination has recently been reported ⁵⁸. 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 ⁷⁶ (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.

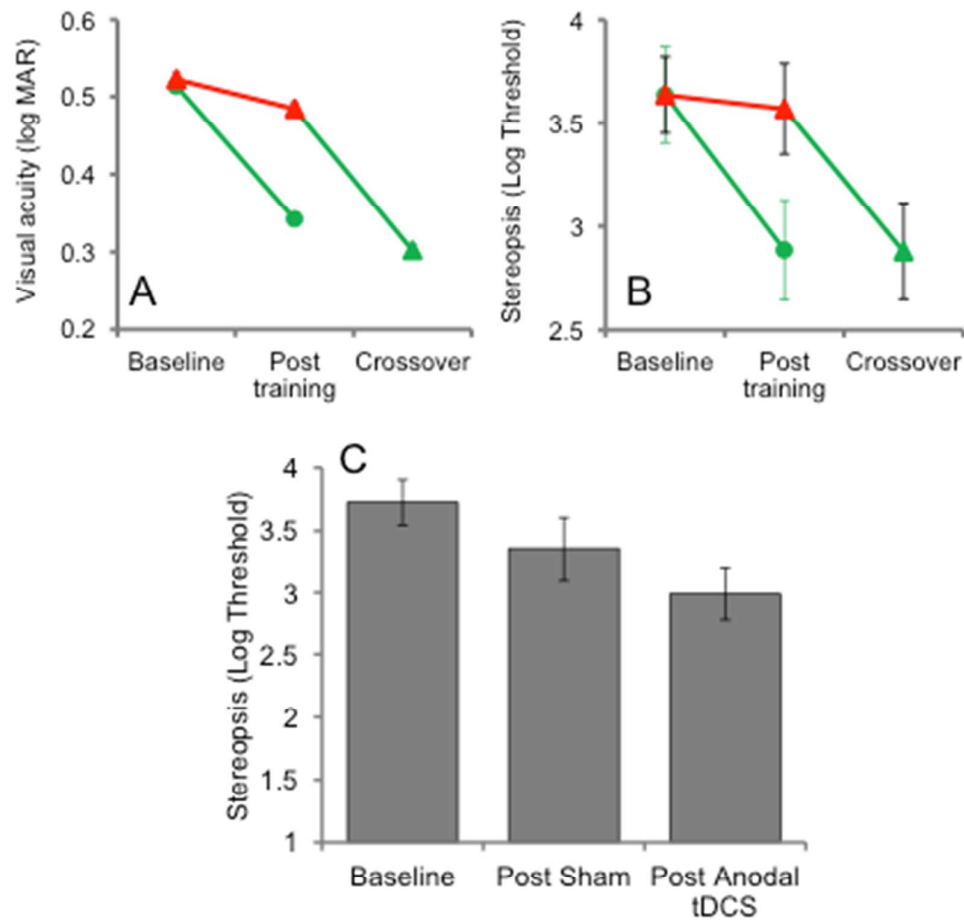


Figure 10. A direct comparison between two weeks of monocular Tetris play (red lines) and dichoptic Tetris treatment (green lines) in 18 adult amblyopes ($n = 9$ adults per group, panels A and B). Dichoptic treatment resulted in far greater improvements in acuity (panel A) and stereopsis (panel B) than 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 ^{58, 76}.

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.
7

8 5. Conclusions

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10 A number of conclusions may be drawn from the evidence presented in the
11 preceding sections. Firstly, visual function in the amblyopic eye is limited by
12 the weak and noisy nature of inputs from this eye to the visual cortex as well
13 as suppression of these inputs by information from the fellow eye, although
14 there is still much to learn about the connection between these two
15 phenomena. Crucially, when these impediments to visual function are
16 accounted for, intact binocular mechanisms are revealed. Secondly, the
17 strength of binocular combination (or the reciprocal; the strength of amblyopic
18 eye suppression) can be objectively quantified using psychophysical tasks
19 that target the primary visual cortex as well as dorsal or ventral extrastriate
20 areas. The measurements reveal that stronger suppression is associated with
21 poorer visual function in amblyopes and that suppression can be modulated in
22 both amblyopes and observers with normal vision using partial occlusion
23 techniques and, unexpectedly, short term occlusion of the weaker eye.
24 Thirdly, dichoptic perceptual learning, designed to strengthen binocular
25 combination by reducing suppression, improves both stereopsis and acuity in
26 adults and children with amblyopia. These effects can be enhanced by non-
27 invasive brain stimulation techniques which can also improve contrast
28 sensitivity in their own right, possibly by reducing suppression of inputs from
29 the amblyopic to the cortex. As a whole, these results lead us to question the
30 prevalent view that amblyopia is primarily a disorder of monocular vision and
31 should be treated accordingly with monocular occlusion. If we are open to the
32 possibility that binocular interactions lie at the heart of amblyopia, then we
33 could be at the threshold of a new age of therapeutic interventions that don't
34 involve patching the fellow fixing eye.
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39 6 Acknowledgements

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