OPO OPHTHALMIC & PHYSIOLOGICAL OPTICS
THE JOURNAL OF THE COLLEGE OF OPTOMETRISTS

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Journal:	*Ophthalmic and Physiological Optics*
Manuscript ID:	OPO-IR-1216
Manuscript Type:	Invited Review
Date Submitted by the Author:	18-Sep-2013
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Keywords:	binocular vision, amblyopia, suppression, treatment

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 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 [1]. However, amblyopia is characterized by a range of visual deficits that affect both monocular and binocular visual function [2]. 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 reduced [5-8]. Many researchers concluded from this that binocular combination simply did not occur in amblyopes, consistent with early physiological work on cats with surgically induced strabismus [9]. 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 work [6] 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 [11] repeated the experiment on a larger number of amblyopes with varying aetiologies. Some of their results resembled those of

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

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

2.3 Noise masking in amblyopia

By adding external noise to a stimulus, an estimate of the internal noise in the detecting channel can be obtained when the external noise is of sufficient contrast to raise detection thresholds [17]. Several studies have applied this paradigm to compare the level of internal noise across amblyopic and fellow eyes within individual observers. One such study [18] found clear evidence for increased internal noise in two of their four observers, with the remaining two observers showing a pattern more consistent with poor information extraction (calculation efficiency). For letter identification though, little increase in internal noise was found , but much poorer calculation efficiency was evident[19].

External noise studies using more sophisticated techniques (e.g. classification image and double pass methods) have also concluded that internal noise is elevated in the amblyopic eye [20-22] though it is unclear whether this is additive, multiplicative or both [12, 21]. Increased noise at the psychophysical level might be caused by fewer active neurons (leading to lower signal to noise ratios) or inappropriate connections between neural populations. Evidence favouring the latter possibility was reported [23], though this conclusion was based in part on the lack of a difference in contrast discrimination performance between amblyopic and fellow eyes in their observers. As detailed in section 2.2, other studies have found a substantial difference on this task [12-14], so both explanations may be correct.

2.4 Perceived phase and perceived contrast

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

2.5 Models of amblyopia

Baker et al. [12] took a model developed to explain normal binocular combination [4] and asked how it needed to be changed to account for the pattern of contrast discrimination functions measured from 8 strabismic amblyopes. They considered several 'lesions' to the model, including absent binocular combination, and suppression from the fellow eye onto the amblyopic eye. Surprisingly, these two modifications were unable to account for any of the key features of the data. Instead, a very different picture developed of the architecture of the amblyopic visual system. In the most successful model, binocular combination and interocular suppression are normal. However, the input to the amblyopic eye is attenuated at an early stage, and subject to increased levels of noise. These two small modifications correctly predicted all of the main findings from that study. However the fact that increased suppression was not required was a consequence of the pedestal masking paradigm used in this study and does not imply that it is absent.

Huang et al. [26, 27] made similar modifications to the binocular model of Ding and Sperling [24] to account for their phase and contrast matching data in amblyopes. They confirmed the importance of monocular attenuation with intact binocular combination, and also found evidence for increased interocular suppression. Ding et al.[25] made further refinements to the gain properties of this class of model to account for several subtle patterns in their data.

2.6 Interim summary

We can extrapolate from these studies some general points about contrast vision in amblyopia. First, binocular mechanisms do appear to exist in the human amblyope, and involve both summation and suppression of signals across the eyes. But the amblyopic signal is weaker, noisier, and may be

strongly suppressed by signals in the fellow eye. These factors combine so that, for typical high contrast scenes, most of the information available to the observer comes from the fellow eye. So, amblyopes can be *structurally* binocular, yet appear *functionally* monocular, in that they base their responses in natural viewing tasks on the input from the fellow eye.

3. Suppression

3.1 History

As descried above, suppression within the context of binocular vision refers to an inhibitory influence of the fellow eye over the amblyopic eye when both eyes are viewing. It has been assumed that the role of suppression is to stop information from the amblyopic eye reaching perception to prevent visual confusion or diplopia. However, evidence for this assumption within clinical research is mixed at best. Initially in the 1950s and 1960s suppression was a hot topic and the work of Travers[28] in Melbourne, Pratt-johnson[29] in the UK and Jampolski[30] in the USA stand out. They carefully plotted suppression scotomata and related their size and position in different forms of strabismus. There was a consensus that the scotomata were localized and involved the region of the visual field in the deviated eye that corresponded to the fovea in the fixing eye, sometimes extending to include the foveal region of the deviating eye. In the following 3 decades, interest in suppression waned and while its presence may have been documented in clinical examinations, not much use was made of it. More recently, there has been a revival in research into suppression which involves new and much less dissociative ways of measuring it [31-33] and treatment interventions which directly target suppression (described in section 4). For many, suppression is the enemy in terms of restoring binocular function and its elimination is a necessary first step in any binocular therapy[34-36]. For others who worry about the possibility of producing diplopia, suppression is their friend, ensuring that when both eyes are open there is only vision from one eye. In a lot of ways we are still in the dark ages when it comes to suppression, opinions rage for and against its elimination, but little evidence is furnished to support either camp. The renaissance in thinking about suppression only came when we developed a means of numerically quantifying its strength. Once we had a number, rather than a binary on/off measure, we could ask questions that are addressed in detail below such as; *how does suppression vary in amblyopia?, how is suppression distributed across the visual field? Is suppression similar in strabismics and ansiometropes?, and how can we modulate suppression?*

3.1. Methods of measuring suppression. Understanding of suppression has been impeded by the lack of quantitative measures as most clinical tests, such as the Woth 4 Dot test, only indicate whether suppression might or might not be present. Recently, a number of different tests have been devised, two based on global processing (form and motion) and another involving local phase and contrast (Figure 1).

3.1.1. The motion coherence test (Figure 1A). This test involves the dichoptic presentation of noise elements (having a random motion direction) to one eye and signal elements (having the same coherent motion direction) to the other eye[37]. The noise presented to one eye makes it more difficult to detect the direction of the signal in the other eye. In binocularly normal individuals with no strong dominance, it does not matter which eye sees the signal and which eye sees the noise; the dichoptic interactions are balanced [38]. However, this is no longer the case in amblyopes. Owing to suppression, performance is better when the noise is presented to the "suppressed" amblyopic eye and worse when signal is in the amblyopic eye. Suppression can be measured by assessing how much the contrast of the stimulus presented to the fellow fixing eye has to be reduced to reach a point where it does not matter which eye sees the signal and which sees the noise, task performance is equal. This can only occur when information from the two eyes is combined equally and, being a global motion task, this approach involves an assessment of suppression which relies on dorsal extra-striate function. In the original version[37] of this technique, blocks of signal to one eye and noise to the other eye were presented using randomly interleaved staircases. An abbreviated version involves the presentation of signal to the amblyopic eye and noise of variable contrast to the fellow eye [39]. More recently, we have devised a version of the test specifically for high anisometropes in which dot size is randomized to ensure that anisokenia does not provide a cue for signal noise segregation [40] .

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

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

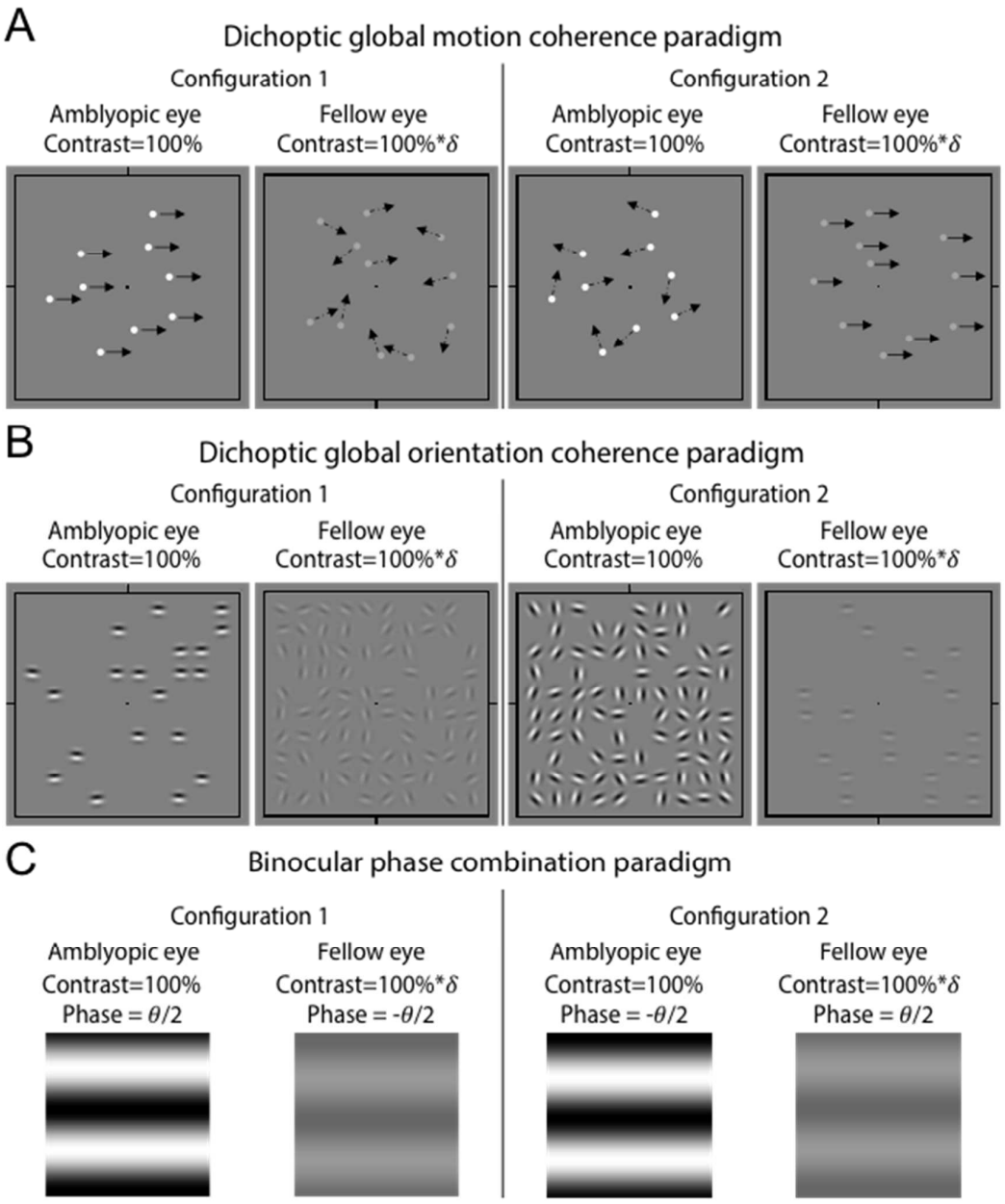

Figure 1. An illustration of the stimuli and paradigms used to measure interocular suppression. (A) The dichoptic global motion coherence paradigm. (B) The dichoptic global orientation coherence paradigm. (C) The binocular phase combination paradigm. See sections 3.1.1 to 3.1.3 for further details.

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[43] which involved 9 patients of whom 1/3 were alternating strabismics. Alternating strabismics typically have suppression (which may be very strong [44]) 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[45] 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].

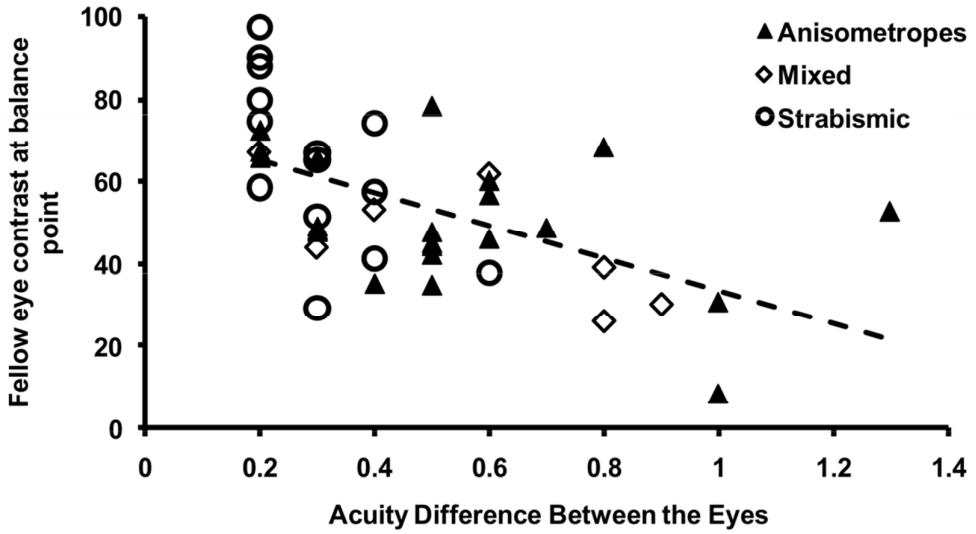

Figure 2. Mean fellow eye contrast at balance point as a function of interocular acuity difference (Log MAR) for 43 patients with amblyopia. Lower values on the Y axis indicate stronger suppression (see section 3.2 for details). There was a significant negative correlation ($p < 0.001$) indicating that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

3.3. The regional distribution of suppression

Since the work of Travers[28], Jampolski[30] 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 means[49] 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.

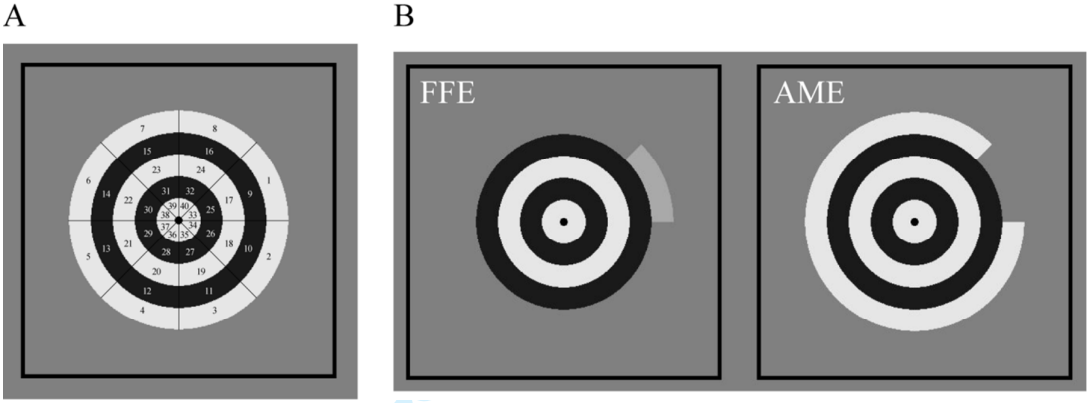

Figure 3. The annular-based suppression mapping stimulus. Panel A depicts the 40 regions of the visual field that were tested. The radius of the most eccentric ring is 10°. Panel B depicts the dichoptic testing arrangement. One segment was shown to the fellow eye and the remaining segments from the same 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[49].

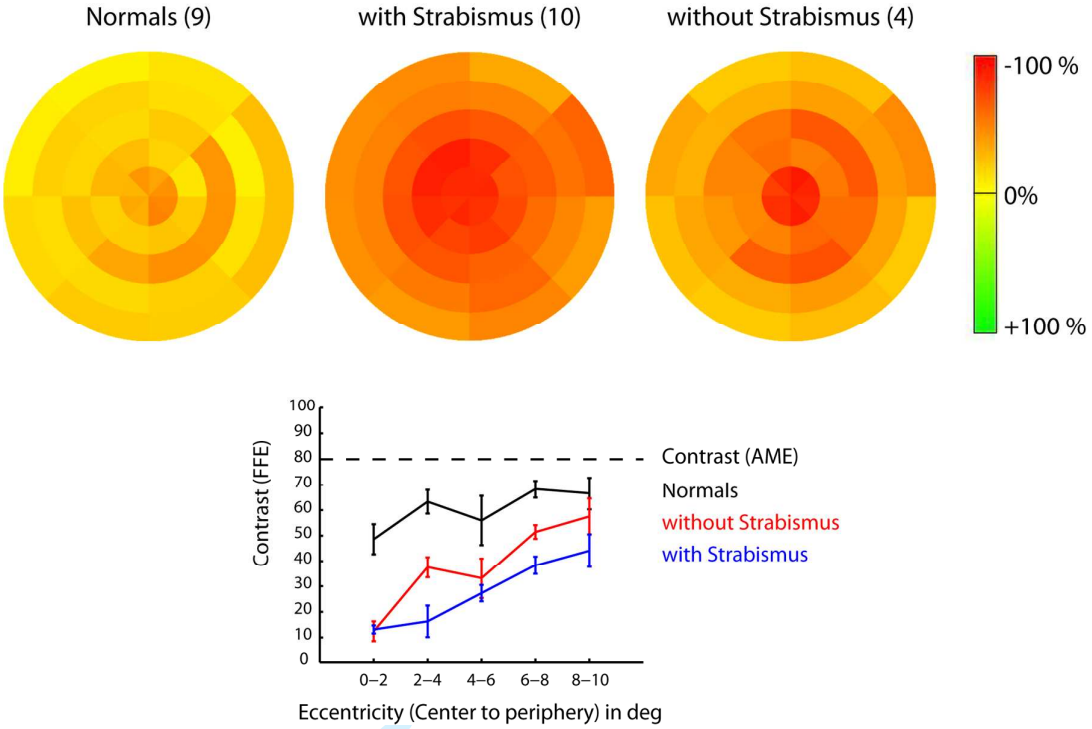

Figure 4. Average suppression maps for observers with normal binocular vision (n = 10) and amblyopes with (n = 10) and without (n = 4) strabismus. Amblyopia is associated with significantly stronger suppression than that found in normals. The color maps indicate the magnitude and extent of suppression 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 rivalry[50] whereby the image shown to the previously patched eye becomes dominant. We investigated this effect further [51] using the motion coherence test[37], the phase test[26] and the dichoptic contrast test[26] and found good support for this novel phenomenon. Examples of the results for the phase and motion coherence tests are shown in Figure 5.

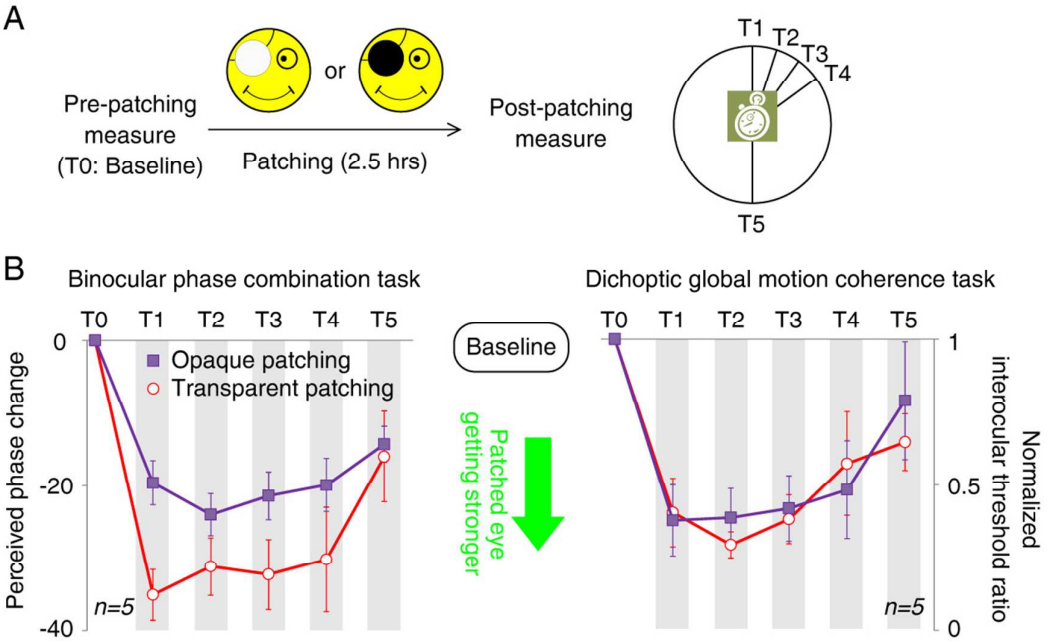

Figure 5. The effect of 2.5 hrs of monocular occlusion with either a light-tight patch or a diffuser on the binocular phase combination task and the dichoptic global motion coherence task. (A) Experimental protocol, (B) Patching effects on the binocular phase combination task (left panel) and dichoptic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

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[51].

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.

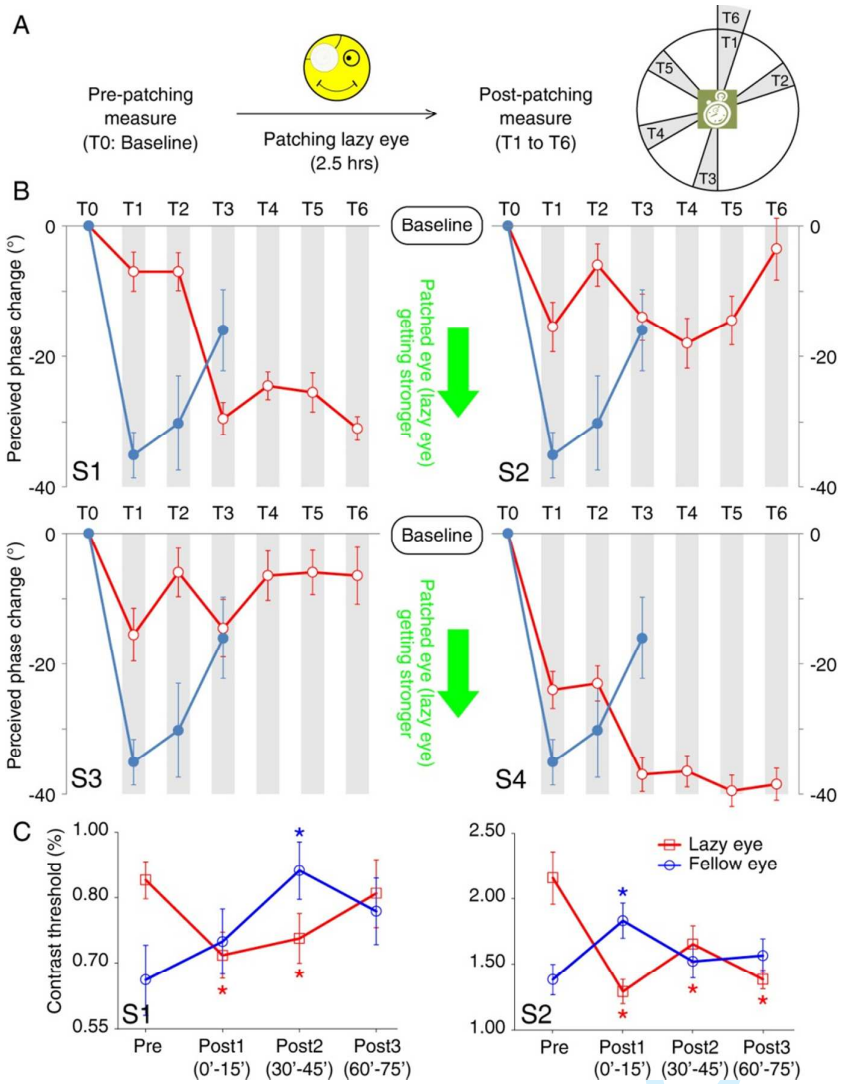

Figure 6. a) The time line of the patching and testing protocol. b) Measurement of binocular balance using the phase test after patching of the amblyopic eye for each of 4 observers with amblyopia (S1-S4). The red lines with open dots in each panel represent the time course of the perceived phase change 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[52].

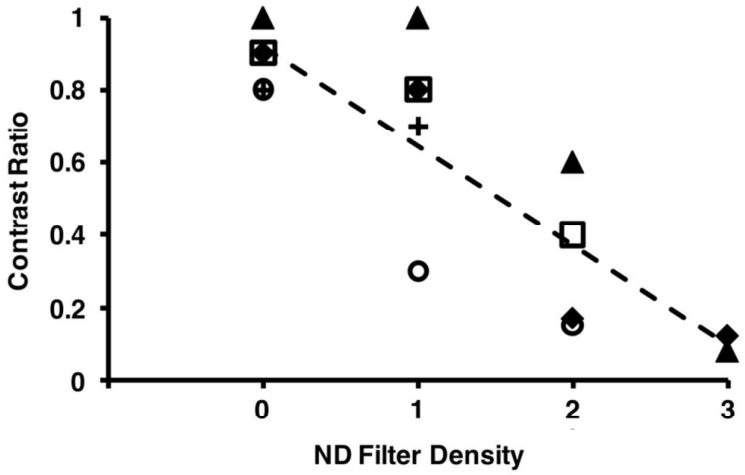

Figure 7. The contrast ratio between the eyes on the dichoptic global motion coherence task as a function of the strength of neutral density filter placed over the non-dominant eye for observers with normal binocular vision. A ratio of 1 on the Y-axis indicates normal binocular combination. Lower ratios 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 filer strengths require greater contrast imbalances to achieve normal binocular combination. Each symbol represents a different observer. From[52].

Figure 7 shows measurements of binocular balance in terms of the contrast ratio for the signal and noise within the dichoptic motion coherence task[37]. 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[53]. Similarly, in amblyopia where there is an initial imbalance of the inputs of the two eyes due to

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

3.5 Interim summary

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

4. Suppression as a target for amblyopia treatment

Evidence presented in the preceding sections supports the idea that individuals with amblyopia have the capacity for binocular vision, but that this capacity is suppressed under normal viewing conditions. Furthermore, it appears that suppressive or inhibitory interactions within the visual cortex may play a central role in the loss of both monocular and binocular vision that characterizes amblyopia. Stronger suppression is associated with poorer stereopsis and poorer amblyopic eye visual acuity in humans[40, 45-47] and compelling links between suppression and visual dysfunction have been found in animal models of amblyopia and strabismus [55, 56]. Initial evidence also indicates that stronger suppression is associated with a poorer response to occlusion therapy in children [47], even when factors such as pre-treatment visual acuity and stereopsis are accounted for [46]. This raises the possibility that suppression not only masks latent visual capabilities [57] but also gates visual cortex plasticity[58]. In this context, interventions that directly target suppressive interactions within the visual cortex may be particularly relevant

to the treatment of amblyopia. New treatments for amblyopia are highly desirable as current treatments, whilst effective at improving amblyopic eye acuity, are not ideal (see [59] for a recent discussion of the issues involved).

4.1 Non-invasive brain stimulation and amblyopia

Non-invasive brain stimulation techniques can be used to modulate fundamental properties of neural systems such as excitation and inhibition [60]. These techniques have been intensively studied in the context of neuro-rehabilitation as abnormal patterns of inhibition and excitation have been implicated in a wide range of neurological disorders. For example, beneficial effects of non-invasive brain stimulation have been reported for disorders such as depression, stroke, tinnitus, Parkinson's disease and chronic pain[61-65]. The two most prevalent forms of non-invasive brain stimulation are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). TMS involves the generation of brief, targeted magnetic fields which pass harmlessly through the scalp and generate a weak electrical current in the underlying region of cortex[16, 66]. When multiple pulses of TMS are administered in close succession, either as a train of pulses (a technique known as repetitive TMS or rTMS[67]) or a series of "bursts" (e.g. theta burst stimulation or TBS[68]), the stimulation can transiently alter excitation and inhibition within the stimulated region. tDCS involves the use of a weak (1 or 2 mA) direct current passed between two large head-mounted electrodes positioned over the brain regions to be stimulated. Cathodal stimulation tends to decrease excitability of the stimulated neural population whereas as anodal stimulation often has the opposite effect[69]. rTMS, TBS and tDCS are effective when delivered to the visual cortex modulating factors such as contrast sensitivity, motion perception, visual evoked potentials and phosphene thresholds (the intensity of a single pulse of TMS delivered to the occipital lobe required to induce the percept of a phosphene; a measure of visual cortex excitability) [70-75].

A series of recent studies have investigated the possibility that non-invasive stimulation of the visual cortex can improve vision in adults with amblyopia [76-79]. The rationale for applying non-invasive brain stimulation to amblyopia is manifold. Firstly, rTMS, TBS and tDCS have been shown to modulate abnormal inter-hemispheric patterns of suppression/inhibition within the human motor cortex suggesting that these techniques can reduce pathological suppression[62, 80]. Secondly, the effects of brain stimulation have been shown to interact with ongoing neural activity within the stimulated brain region. This allows for distinct neural populations to be targeted even when the populations inhabit the same region of stimulated cortex [81]. In particular, brain stimulation may act to restore homeostasis to neural populations[82]. This is relevant to amblyopia as the resolution of brain stimulation does not allow for separate ocular dominance columns to be targeted, however the stimulation may differently affect neural inputs from the amblyopic and fellow eye by virtue of their differing levels of excitation and inhibition (as described in the sections above). Thirdly, brain stimulation techniques may act to reduce intra-cortical inhibition[67] which has been strongly implicated as a "break" on visual cortex plasticity in animal models of amblyopia[83]. Finally, anodal tDCS

in particular has been shown to reduce GABA levels within the human motor cortex[84] and behavioral evidence suggests that similar effects may occur within the human visual cortex[85]. This is of interest in the context of amblyopia as GABA is thought to play a key role in suppression of inputs from the amblyopic eye within the visual cortex[56]. We therefore hypothesized that non-invasive brain stimulation may reduce suppression of inputs from the amblyopic eye within the visual cortex and/or enhance visual cortex plasticity.

Current evidence is generally consistent with this hypothesis (Figure 8). Specifically, we have shown that non-invasive brain stimulation can improve contrast sensitivity in at least a subset of adults with amblyopia. In the first study to address this question we measured contrast sensitivity for low and high spatial frequency Gabor targets (the exact spatial frequency was tailored for each patent) before and after an inhibitory rTMS protocol (1Hz stimulation, n = 9 patients) and an excitatory protocol (10Hz stimulation, n = 6 patients) delivered to the primary visual cortex[79]. Stimulation of the motor cortex was used as a control condition. Both types of rTMS resulted in significant improvements in contrast sensitivity (a mean improvement of approximately 40%) when high spatial frequency targets were viewed by the amblyopic eye (7/9 patients improved for 1Hz and 6/6 for 10 Hz, including the two patients who did not improve for 1Hz). No improvements were found for the low spatial frequency target for which the amblyopic eyes did not show a pronounced contrast sensitivity deficit at baseline. Furthermore, improvements were not found for the fellow eye after visual cortex stimulation or for either eye after motor cortex stimulation, indicating that the rTMS effects specifically targeted amblyopic eye function. The improvements were transient however, with thresholds returning to baseline within approximately 24 hours after stimulation. In a follow-up study we investigated the effect of repeated administration of rTMS (in this case continuous TBS; cTBS) over five consecutive days in four adults with amblyopia[78]. The acute effects of a single stimulation session (measured in 5 patients) resulted in improvements in contrast sensitivity for the amblyopic eye of a similar magnitude to the original study. Furthermore there was a cumulative effect of cTBS on contrast sensitivity over the first two sessions which stabilized over subsequent sessions and endured for up to 78 days.

Improvements in contrast sensitivity have also been found in a subset of adults with amblyopia after anodal tDCS of the visual cortex (20 minutes at 2mA) [77]. Of 13 adults tested, 8 showed improvements in amblyopic eye contrast sensitivity after anodal tDCS (an average of 27% improvement) whereas 5 showed the opposite effect. No reliable improvements for either group were found for amblyopic function after cathodal stimulation or for the fellow fixing eye. Previous studies applying anodal tDCS to other neurological disorders have also reported groups of responders and non-responders [86] suggesting that this type of brain stimulation may only be of use for a subset of participants. To ensure that anodal tDCS was having an effect on the visual cortex, fMRI measurements of visual cortex activation in response to counter-phasing checkerboard stimuli presented to either the amblyopic or non-amblyopic eye were made after real and sham anodal tDCS in a group of responders (n = 5). After sham tDCS there was a greater response

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 V3[77]. 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 in interactions within the visual cortex.

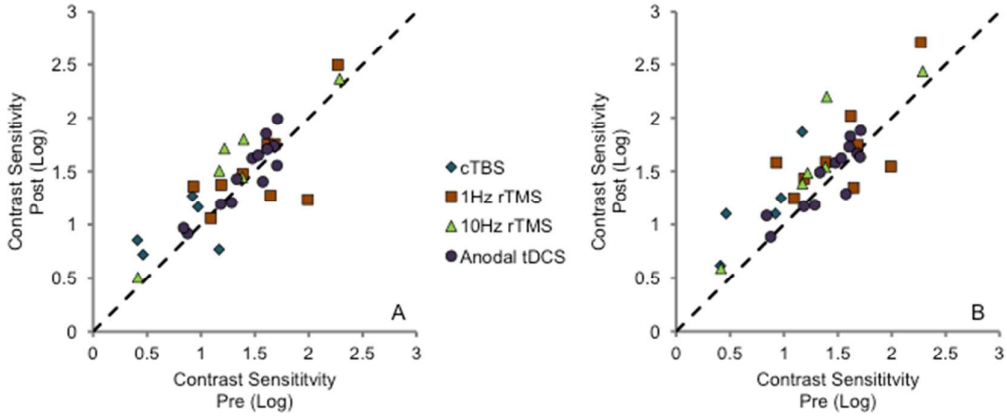

Figure 8. A comparison of log contrast sensitivity for a fixed high spatial frequency before, after (panel A) and 30 minutes after (panel B) different types of non-invasive stimulation of the visual cortex (continuous theta burst; cTBS, 1Hz and 10Hz repetitive transcranial magnetic stimulation; rTMS, 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 [77-79].

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

weeks[34, 35]. At the end of the study 6/9 participants no longer needed a contrast difference between the two eyes to allow for normal binocular combination of the signal and noise. Furthermore, visual acuity improved by an average of 0.26 LogMAR (95% CI 0.15 to 0.37 LogMAR, Figure 9 diamonds) and 8/10 patients improved in stereopsis with 6 patients going from no measureable stereopsis on the RanDot test to stereopsis in the range of 200-40 seconds of arc. These effects were striking as at no point during the study was the fellow eye patched. The transfer of the training effect from the dichoptic global motion task to improved monocular and binocular visual function in these adult patients suggested that suppression of the amblyopic eye may play a causal role in amblyopia and that reducing suppression enabled plasticity with the visual cortex.

In order to translate these results into a clinical context we incorporated the dichoptic contrast offset technique into a version of the videogame Tetris which requires players to tessellate falling blocks together. Some blocks are shown to the amblyopic eye at high contrast and others to the fellow eye at a low contrast tailored to each patient's level of suppression. Both eyes must be used simultaneously to play the game and successful game play results in a reduction of the contrast difference between the two eyes. This game has been deployed on a pair of video goggles with a separate screen for each eye and portable iPod Touch and iPad devices for which dichoptic viewing is enabled using either a lenticular overlay screen or red/green anaglyph glasses. To date there are 63 published cases of patients treated using the Tetris method with ages ranging from 5 to 51 years and treatment duration ranging from 5 hours to 40 hours [88-93]. Across studies the average improvement in amblyopic eye visual acuity was 0.21 LogMAR (95% CI 0.17 to 0.25 LogMAR) and 42/63 patients (67%) of patients improved in stereopsis with 15/63 patients (24%) recovering stereo after treatment having no measureable stereo pre-treatment. Acuity and stereopsis improvements for all published cases treated with either the dot stimulus or the Tetris videogame are shown in Figure 9. A univariate ANOVA conducted on the change in LogMAR amblyopic eye acuity from pre to post treatment with factors of amblyopia type (anisometropic vs. strabismic vs. mixed), age and treatment duration in hours revealed no significant main effects or interactions. In addition, the proportion of patients who improved in stereopsis was similar across the amblyopia subtypes of anisometropic (10/32 improved, 31%), strabismic (7/19, 37%) and mixed (4/11, 36%). Therefore these initial data suggest that the effect of the treatment is independent of age and amblyopia subtype. Randomized clinical trials are currently underway to assess the efficacy of this treatment approach in larger groups of patients.

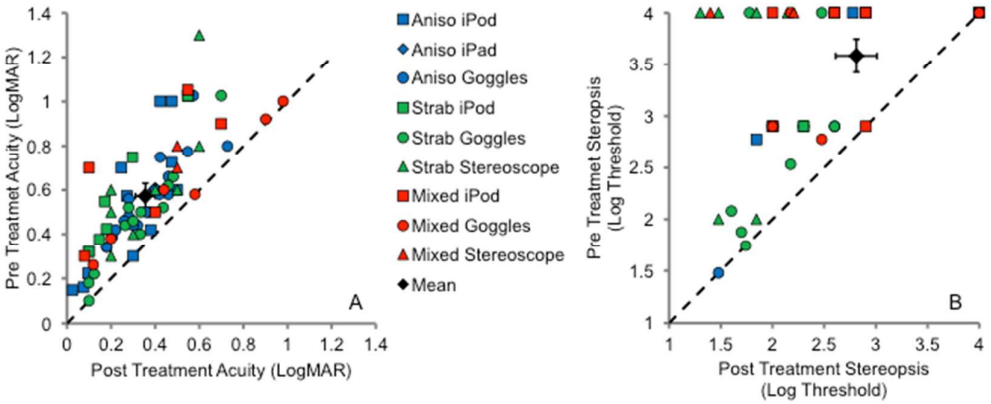

Figure 9. Improvements in amblyopic eye visual acuity (A) and stereopsis (B) for the 73 published cases of amblyopia treated using the dichoptic contrast balanced approach (either global motion or Tetris). Data points above the unity lines indicate improvements. Participants treated with the stereoscope 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.

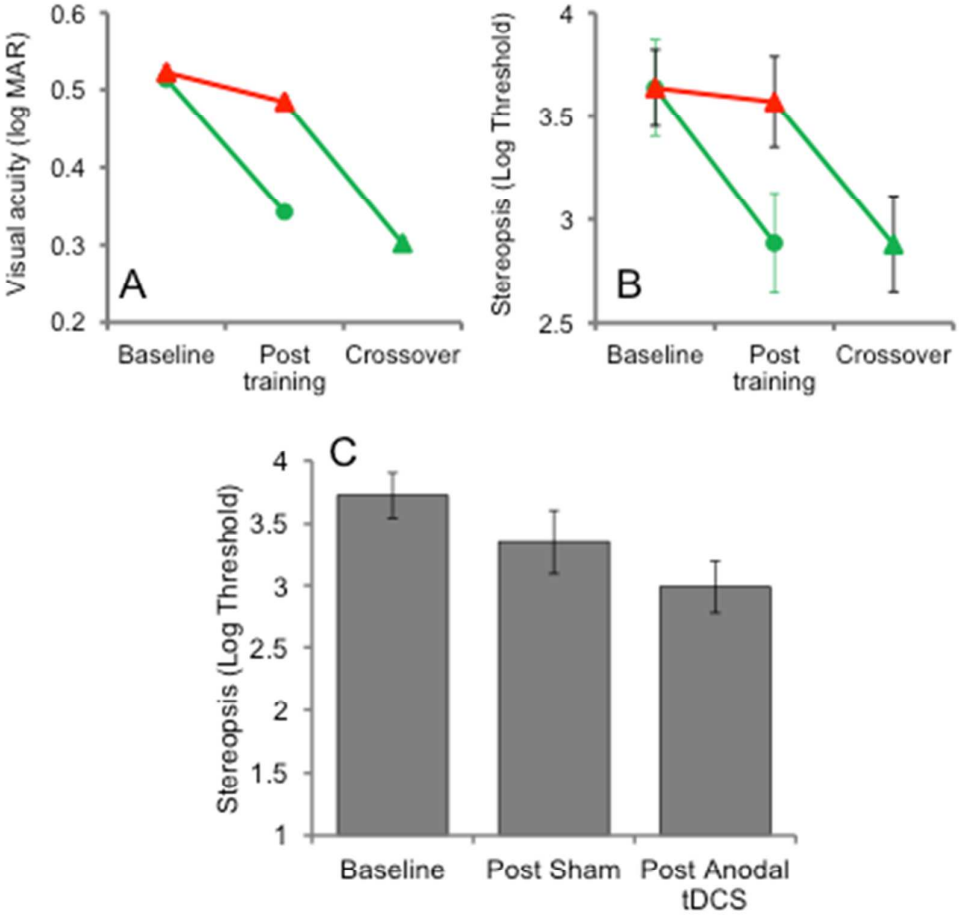

Figure 10. A direct comparison between two weeks of monocular Tetris play (red lines) and dichoptic Tetris treatment (green lines) in 18 adult amblyopes (n = 9 adults per group, panels A and B). Dichoptic treatment resulted in far greater improvements in acuity (panel A) and stereopsis (panel B) than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

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

5. Conclusions

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

6 Acknowledgements

BT is supported by grants from the Health Research Council of New Zealand, The Marsden Fund and the University of Auckland. RFH is supported by CIHR grants (#53346, 108-18 & 93073).

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