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A new binocular approach to the treatment of Amblyopia in adults well beyond the critical period of visual development

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Abstract. *Background:* The present treatments for amblyopia are predominately monocular aiming to improve the vision in the amblyopic eye through either patching of the fellow fixing eye or visual training of the amblyopic eye. This approach is problematic, not least of which because it rarely results in establishment of binocular function. Recently it has shown that amblyopes possess binocular cortical mechanisms for both threshold and suprathreshold stimuli.
Objectives: We have outline a novel procedure for measuring the extent to which the fixing eye suppresses the fellow amblyopic eye, rendering what is a structurally binocular system, functionally monocular.
Results: Here we show that prolonged periods of viewing (under the artificial conditions of stimuli of different contrast in each eye) during which information from the two eyes is combined leads to a strengthening of binocular vision in strabismic amblyopes and eventual combination of binocular information under natural viewing conditions (stimuli of the same contrast in each eye). Concomitant improvement in monocular acuity of the amblyopic eye occurs with this reduction in suppression and strengthening of binocular fusion. Furthermore, in a majority of patients tested, stereoscopic function is established.
Conclusions: This provides the basis for a new treatment of amblyopia, one that is purely binocular and aimed at reducing suppression as a first step.

Keywords: Amblyopia, global motion, contrast, binocular summation, dichoptic interaction, treatment of amblyopia

1. General Introduction

Amblyopia is a disorder in which the vision in one eye fails to develop in early childhood. The incidence of amblyopia is high (3%) and it is associated with either a strabismus (turned eye) or anisometropia (unequal refractive error) or both. The most common treatment directed at recovering monocular function involves patching the good eye in an effort to force the amblyopic eye to improve. In a limited number of cases there is an improvement in monocular vision though rarely does this follow through into improved binocular function (P.E.D.I.G., 2005). In fact amblyopia, particularly strabismic amblyopia, has a significant rate of recurrence (27%) after patching treatment is stopped (Bhola et al., 2006). This treatment has a low compliance because it forces children to live in the partially sighted world of their amblyopic eye (P.E.D.I.G., 2005). As a consequence it has a well-documented history of psycho-social side-effects (Searle et al., 2002). This is an important problem not only from the visual perspective but also because it has its effect during the early intellectual and psychological development of children. There is a need for a better approach, one that will be more effective in children, one that might be applicable to the many adults who have been left permanently visually disabled and whose treatment has been abandoned (Epelbaum et al., 1993), one that might promote cooperation between the two eyes with the eventual hope of establishing some rudimentary form

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of depth vision and one that will not have the adverse psycho-social side-effects of the present approach.

Our ideas on the binocular status of strabismic amblyopes are undergoing change. We now know that the loss of the binocular responsiveness of cortical cells in strabismic animals is largely reversible (Mower et al., 1984) by ionophoretic applications of bicuculline (selective blocker of GABAA receptors), suggesting an active suppression rather than a loss of cellular function (Sengpiel et al., 2006). Furthermore, there is reason to doubt the claim that amblyopes don't possess binocular mechanisms since Baker et al. 2007 (Baker et al., 2007) showed normal binocular contrast summation in strabismic amblyopes when the signal attenuation by the amblyopic eye is taken into account, suggesting that the lack of summation found previously was due to the imbalance in the monocular signals prior to the point of summation. Taken together, this suggests that strabismic amblyopes do have binocular mechanisms similar to that of anisometropic amblyopes where it has been shown that active anti-suppression training regimes can be successful even for patients older than 10yrs(Wick et al., 1992). The realization of the importance of suppression in the poor acuity and binocular function of strabismics is well known by some (Jampolsky et al., 1985) but at present it is not reflected in clinical practice. More recently, it has been shown that the reason why binocular combination does not normally occur for suprathreshold motion and orientation tasks in strabismic amblyopia is because of interocular suppression (Mansouri et al., 2008). A reduction of suppression leads to normal levels of binocular combination in strabismic amblyopia, revealing the presence of binocular cortical mechanisms. Finally, it has been shown that the monocular vision of adults with amblyopia can be improved after only 10 minutes of repetitive transcranial magnetic stimulation (rTMS) to the visual cortex (Thompson et al., 2008). Since rTMS is known to modulate inhibitory interactions within the human cortex (Modugno et al., 2003, Pascual-Leone et al., 1998) this suggests a significant part of the monocular loss may be suppressive in nature. Thus there is converging evidence for the conjecture that strabismic amblyopes, like their anisometropic counterparts (Wick et al., 1992) possess cortical cells with binocular connections but that under binocular viewing suppressive mechanisms render the cortex functionally monocular. In turn this suggests that amblyopia is an intrinsically binocular problem and not the monocular problem on which the present patching treatment is predicated. Thought of in this way, the binocular problem involving suppression should be tackled at the very outset if one is to achieve a good binocular outcome, as opposed to hoping binocular vision will be regained simply as a consequence of acuity recovery in the amblyopic eye, which is the current approach and which is often not successful (Mitchell et al., 1983).

Recently, we developed a novel way of quantifying suppression (Mansouri et al., 2008). We found, under a wide variety of conditions, that when the signal to the fellow fixing eye is reduced in strength, strabismic amblyopes can combine information between their two eyes, as normal individuals do. The extent to which the signal to the fellow fixing eye needs to be reduced allows one to quantify the degree of suppression. Here we report that continual and intensive measurement of the degree of suppression leads, in itself, to a reduction in the strength of suppression of suppression. In other words, providing artificial viewing conditions under which binocular vision can take place, leads to a strengthening of binocular vision, facilitating its operation under a wider variety of interocular viewing conditions. Eventually binocular combination can occur under more natural viewing conditions when the eyes view objects of the same physical contrast. This finding provides the basis for a new binocularly-based treatment of amblyopia in which the suppressive imbalance is measured and treated as a first step. We found that in many cases the reduction of suppression led not only to a re-establishment of stereoscopic function but also to a reduction in the monocular acuity deficit, attesting to the primal importance of suppression in the amblyopic syndrome.

2. General methods

2.1. Observers

Nine strabismic amblyopic adults (see Table 1) participated in the Experiments. Refraction in all observers was undertaken and vision was corrected to best visual acuity. The "Declaration of Helsinki" was followed and informed consent was obtained from all observers before data collection.

2.2. Dichoptic global motion

The measurement of suppression. To measure the ability of amblyopic observers to binocularly combine motion information we used random dot kinematograms (RDKs) and a coherence motion discrim-

Table 1
The clinical data for the 9 amblyopic subjects who undertook binocular training

Obs	Age	Type	Refraction	LA	Squint	History, stereo
1	47	RE LE strab	Ø Ø	20/20 20/80	ET 1	Detected age 6y, no patching, no surgery, no stereopsis
2	44	RE LE strab	Ø Ø	20/20 20/400	ET 20	Detected age 4y, no patching, no surgery, no stereopsis
3	40	RE strab LE	Plano Plano	20/40 20/20	XT 1	Detected at 8 yrs, patching therapy 6months, no surgery. Stereopsis 100 sec.
4	45	RE LE mixed	−1.75+0.5x90 +1.25DS	20/20 20/63	ET 6	Detected at 11y, no surgery & patching, eye exercise 1–2y, glasses since 12y, no stereopsis
5	40	RE strab LE	+5.00–1.00x180 +0.50DS	20/100 20/20	EX 4	Detected age 10y, patching for 1m, glasses for 1y, no stereopsis
6	33	RE strab LE	−1.00DS −0.50DS	20/80 20/15	ET 4	Detected age 5y, patching for 2y, No surgery, no stereopsis
7	24	RE LE mixed	–0.25 DS +3.50–0.50x180	20/15 20/50	ET 15	Detected age 3y, patching for 4y, and glasses for 8y, no stereo
8	35	RE LE strab	plano plano	20/20 20/125	ET 1	Detected age 8y, Rx at 9 yrs. No patching, no surgery, no local stereopsis
9	49	RE LE strab	+3.00DS +4.00DS	20/15 20/125	XT 2	Detected age 6y, glasses 6y, no other treatment, local stereopsis (200 arc second)

Abbreviations: strab = strabismus; Mixed = strab and aniso; Sq = squint; Ob = observers; RE = right eye; LE = left eye; ET = esotropia; XT = exotropia; ortho = orthotropic alignment; DS = dioptre sphere. The angle of strabismus was measured with the Major Amblyoscope and stereopsis was measured with the Randot test. The squint angle is given in degrees where 1 degree equals 1.75 prism dioptres.

ination task (see (Mansouri et al., 2008) for details). These stimuli are constructed of two populations of moving dots. The 'signal' population consists of dots that all move in the same direction, termed the 'coherent' direction. Conversely, the 'noise' population has no common motion direction, as all the dots move in random directions. The ratio of signal to noise dots required to determine the coherent motion direction is called the motion coherence threshold. The measurement of motion coherence thresholds is a well-studied paradigm with regard to global motion integration (Newsome and Pare, 1988). Therefore, by using these stimuli with signal and noise separated dichoptically, one can assess the degree to which underlying mechanisms combine information from two eyes.

2.3. *Perceptual training*

Dichoptic motion coherence thresholds were repeatedly measured over the course of several weeks. We encouraged participants to attend measurement sessions as frequently as their schedules allowed and to keep returning to the laboratory for as long as possible. We were, however, constrained by the availability of participants (see results section for details). We quantified the amount of training each participant received into training blocks. One block of training constituted 100 threshold measurements (50 with signal presented to the amblyopic eye and 50 with signal presented to the fellow eye). The precise number of individual trials each participant was exposed to varied slightly depending on how long it took the staircases to converge, however a single threshold measurement usually required approximately 60 trials. We chose repeated staircase measurements as the training régime since they rapidly converge towards threshold and therefore the majority of training trials are presented at or very close to threshold. The training therefore tracks any improvement in performance to keep stimulus presentation close to the current threshold. During each block of training a range of contrast ratios were presented. The contrast ratios were chosen to provide a range of contrast differences to the two eyes throughout the training procedure. During training participants received trial-wise feedback.

3. Outcome measures

The primary outcome measure for this study was a change in binocular combination measured objectively using our dichoptic motion coherence threshold technique. Each individual threshold we report in the results section is the average of at least five repeated threshold measurements. Within our population of 9 amblyopic observers the mean intra-observer standard

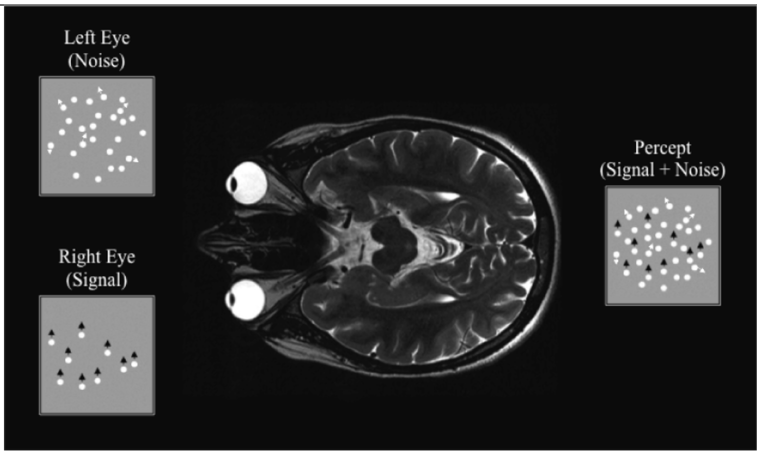

Fig. 1. Illustration of the dichoptic motion stimulus. Elements travelling in a coherent direction ("signal") are seen by one eye and elements travelling in a random direction ("noise") are seen by the other eye. The percept after binocular combination is of signal + noise.

error for this measure across all thresholds was 3.6% coherence (approximately 1 signal dot) for the amblyopic eye (maximum intra-observer standard error was 9.2% coherence or approximately 3 signal dots) and 0.7% coherence (less than 1 signal dot) for the fellow eye (maximum was 1.3% coherence, again less than 1 signal dot) demonstrating that this measure was stable and accurate.

We were also interested in any training-related changes in monocular or binocular function as measured by clinical tests. Monocular visual acuity in both the amblyopic and the fellow eye was measured once a week using a Snellen letter chart and stereoscopic depth perception was measured before and after training using the Randot test. These tests were administered by an experienced clinician who was familiar with the aims of the study. Visual acuity was graded on a line by line basis which allows gross changes in acuity to be identified reliably (Laidlaw et al., 2003). The Randot test is one of a number of available tests for assessing stereoscopic depth perception and although there are issues associated with all clinical tests of this type, hence the need for our new measurement technique (Mansouri et al., 2008), they are the current clinical standard for general assessment of binocular function. The amount of time that participants devoted to this study varied due to individual participant's availability and motivation. The minimum participation time for this study was 2 weeks and the maximum time was 6 weeks. There were also variations in the training "intensity" i.e. how many training sessions took place per week. This was also due to differences in the participant's availability. This variation was incorporated into our analysis (see results section).

4. Results

4.1. Rationale

We have previously used this approach where coherent motion thresholds are measured for dichoptic stimulation (i.e. signal in one eye and noise in the other) to study binocular interactions in normals (Hess et al., 2007) and strabismic amblyopes (Mansouri et al., 2008), performance being quantified by changing the signal to noise ratio. The extent to which information was combined binocularly was quantified by only allowing one eye to see the signal and the other eye to see the noise (see Fig. 1).

In a binocularly normal individual, the noise seen by one eye makes the detection of the motion direction of the signal elements seen by the other eye more difficult. However, it does not matter which eye sees the signal and which sees the noise. There is a "dichoptic balance" in the threshold performance. In amblyopes with suppression, it matters which eye sees the signal and which eye sees the noise. In the most extreme case, if the fellow fixing eye sees the signal and the amblyopic eye sees the noise, then owing to the suppression of the amblyopic eye by the fellow fixing eye, performance will be at ceiling. On the other hand, if the amblyopic eye sees the signal and the fellow fixing eye sees the noise then performance will be at chance. Thus one would expect there to be an imbalance in the dichoptic thresholds due to suppression. By suitably imbalancing the signals seen by the fellow fixing eye (be it signal or noise) we found that balanced dichoptic performance could be obtained reflecting the fact that information from the two eyes was being combined binocularly. In

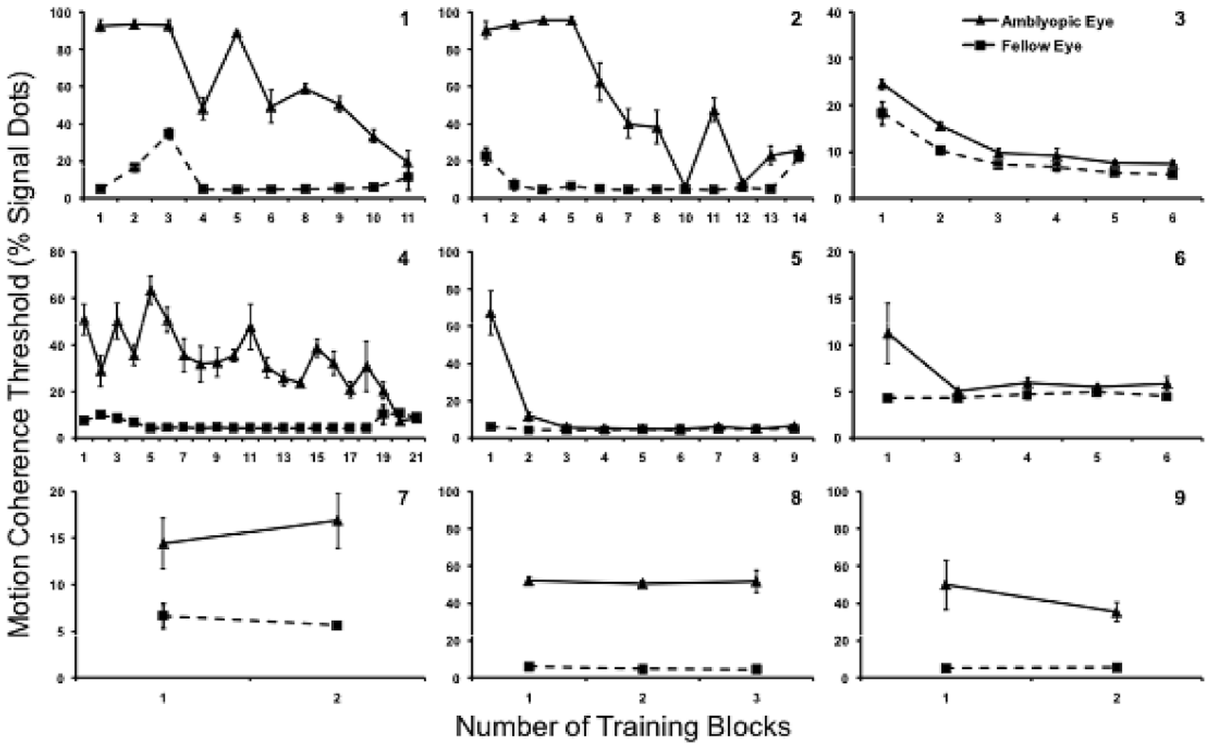

Fig. 2. Change in motion coherence thresholds as a function of number of training blocks for each participant (each block = 100 threshold measurements, approximately individual 6000 trials). Motion coherence thresholds are shown for contrast ratios of 1, i.e. when the same contrast was shown to both eyes. Thresholds are shown for both possible stimulus configurations: signal to amblyopic eye and noise to fellow eye (triangles) vs. signal to fellow eye (triangles) and noise to amblyopic eye (squares). For participants 1 and 2 data points are missing for one block (block 7 for subject 1 and block 9 for subject 2) as thresholds for matched contrast to both eyes were not measured during those specific blocks. Error bars show ± 1 SEM.

other words, imbalancing the *input* to the amblyopic binocular visual system can result in a balanced *output*, namely normal binocular combination. The extent of the signal imbalance needed to achieve this balanced performance provides a measure of the degree of suppression. The presentation was dichoptic (see (Mansouri et al., 2008) for details of stimuli and psychophysical procedures) whereby both eyes viewed a part of the stimulus, either the signal dots or the noise dots, i.e. signal was presented to one eye and noise to the other (see Fig. 1). Since we varied the contrast of the signal and noise independently, we were able to present stimuli with high contrast to the amblyopic eye (AME) and low contrast to the fellow fixing eye (FFE).

To facilitate comparison of training related improvement in task performance between participants we chose to compare task performance for thresholds where the same contrast was presented to each eye (contrast ratio of 1). This is a conservative estimate of improvements in task performance since we would expect suppression to be maximal when the same contrast is seen by both eyes, however this is also the most applicable to everyday viewing conditions where stimuli are not altered in contrast to favour the amblyopic eye.

Figure 2 shows the dichotopic motion coherence thresholds for both the amblyopic and fellow eye as a function of training block number for each participant. It is clear that for the majority of participants (first two rows of panels in Fig. 2) the performance of the two eyes was equated after training. This means that the extent to which the contrast signals in the two eyes need to differ to support binocular vision reduces with practice such that, in some cases, binocular vision can be supported by the natural viewing of everyday images. In this situation, the degree of suppression has been reduced to allow binocular vision to take place for a range of interocular image contrasts not previously possible prior to training. For the participants presented in the bottom row of Fig. 4 training did not appear to improve binocular function as measured by our task. There is a hint of an improvement for subject 9 but this is within the range of the error for the first threshold

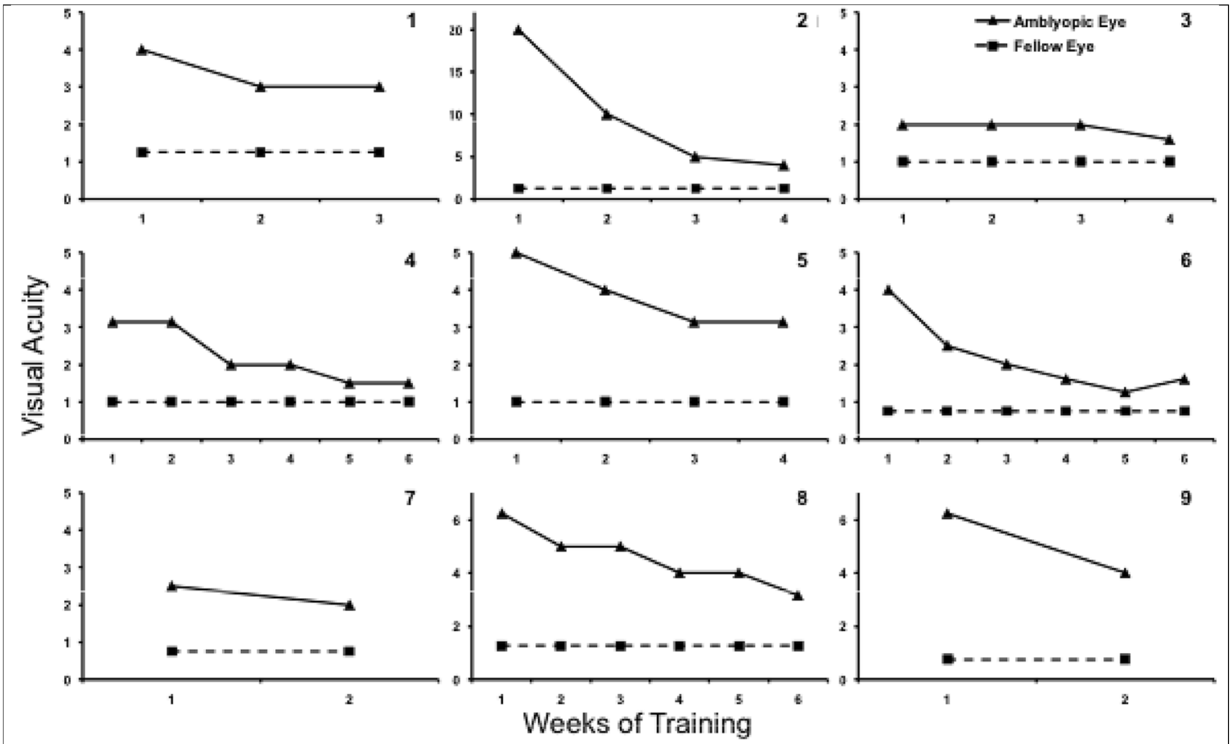

Fig. 3. Change in visual acuity for each participant as measured once per week during training. Triangles show amblyopic eye acuity, squares show fellow eye acuity. Visual acuity is shown in minutes of arc.

measurement. Subject 7 shows the opposite trend and subject 8 shows unchanged performance. It may be the case that since these participants were unable to attend a large number of training sessions, they did not complete a sufficient number of trials to demonstrate an improvement. A consideration of the first three blocks of training for subjects 1 and 2 would support this hypothesis, however as described below we found that training intensity rather then duration of training may be the most important factor for predicting a positive training response. Furthermore, as shown in Figs 3 and 4A, a lack of improvement in dichoptic threshold measures measured for the conservative condition of a contrast ratio of 1, i.e. the same contrast presented to both eyes, did not necessarily prevent improvement in other measures of amblyopic eye function.

On average, training improved amblyopic eye motion coherence thresholds when *the same contrast was presented to both eyes*. A comparison of the motion coherence thresholds under matched contrasts for each eye at the start of training (block one) and at the end of training (number of training blocks varied across participants) using repeated measures ANOVA (degrees of freedom adjusted to account for sphericity using the conservative Greenhouse-Geisser correction) showed that training reduced motion coherence thresholds for both eyes (significant main effect of training [week 1 thresholds vs. final week thresholds], $F[1,8] = 11.3$, $p = 0.01$). In addition fellow eye thresholds were superior to amblyopic eye thresholds (significant main effect of eye, $F[1,8] = 21.0$, $p = 0.002$). Finally, and most importantly, training significantly reduced the difference between the thresholds of the two eyes (significant interaction between eye and training, $F[1,8] = 7.6$, $p = 0.025$). In other words training allowed the amblyopic eye to overcome the suppression of the fellow fixing eye, providing a basis for more normal binocular combination between the two eyes. Post-hoc analysis using paired t-tests revealed a significant difference between week 1 and final week motion coherence thresholds for the amblyopic eye ($t[8] = 3.1$, $p = 0.015$) with no such effect for the fellow eye ($t[8] = 0.6$, $p = 0.57$). It is apparent from Fig. 2 however that improvements in fellow eye thresholds did occur for some participants, particularly subjects 1 and 3. Importantly, there was a significant difference between amblyopic eye and fellow eye thresholds at week 1 ($t[8] = 4.2, 0.003$), an effect that was marginal but non-significant after training

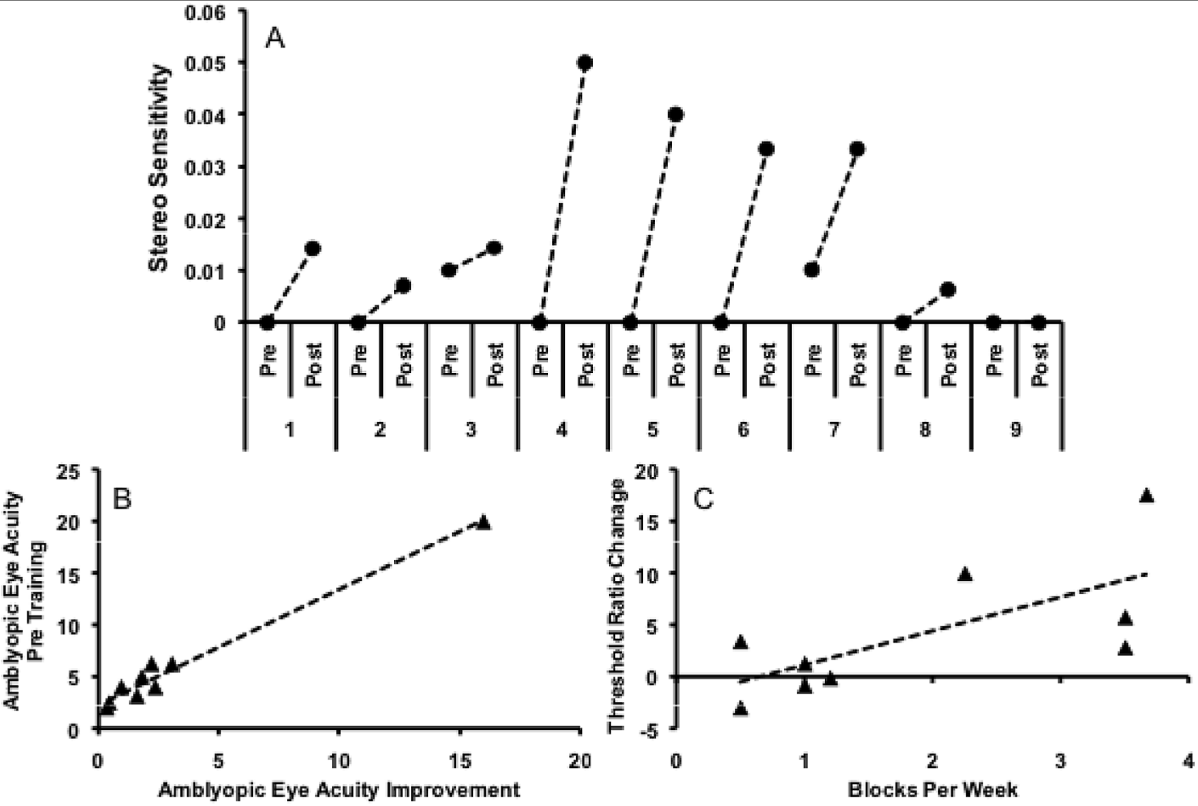

Fig. 4. Panel A shows stereo sensitivity (1/stereo acuity in seconds of arc) measured before (pre) and after (post) training for each individual participant. All but one participant (subject 9) showed an improvement as a result of training. Panel B shows the relationship between the starting acuity of the amblyopic eye and the improvement in amblyopic eye acuity that occurred due to training defined as acuity at week 1 –acuity after training. Panel C depicts the relationship between motion coherence threshold ratio change (see text for definition) and training intensity in blocks per week. The dashed lines in panels B and C represent the best linear fit to the data.

(t[8] = 2.6, $p = 0.066$). This is strong evidence that training improved binocular function to the extent that, as a group, there was no longer a significant difference between AMEs and FFEs after training.

As a consequence of the reduction of suppression and of binocular combination being restored we wondered whether some degree of monocular acuity and/or stereo function might also recover. Encouragingly, we found that the effects of training were not limited to dichoptic motion coherence thresholds. Training significantly improved acuity in the amblyopic eye (Z = 2.7, $p < 0.008$) as can be seen in Fig. 3 which shows improvements amblyopic eye acuity for all participants as a function of number of weeks of training. Some of these improvements are modest (e.g. subjects 7 and 9) but all participants show the same trend of improving amblyopic eye acuity after training. The training also significantly improved stereosensitivity (Z = 2.52, 0.012) as shown in Fig. 4A. Again some changes were modest but it is worth noting that going from no stereo to any kind of stereo function is a significant change in binocular visual function. There was no significant correlation between motion coherence threshold ratio change defined as (amblyopic eye threshold week 1 / fellow eye threshold week1) – (amblyopic eye threshold final week / fellow threshold final week) and improvement in acuity defined as amblyopic eye acuity at week 1 – amblyopic eye acuity final week (Rho[9] = 0.1, $p = 0.8$). The reason for this can be seen from a comparison of Figs 2 and 3, where some participants showed no improvement on the motion coherence task but did show an improvement in amblyopic eye acuity (subjects 7 and 8). Interestingly, as shown in Fig. 4B, the improvement in acuity was positively correlated with the initial starting acuity of the amblyopic eye, i.e. the greater the amblyopic eye acuity loss prior to training, the greater the potential for functional recovery (Rho[9] = 0.9, $p = 0.001$). It is clear from Fig. 4B that one participant (subject 2) had a much greater acuity loss than the other participants and showed the greatest amblyopic eye acuity improvement. The correlation still held however when subject 2 was excluded from the analysis Rho[8] = 0.8, $p = 0.009$. There were no reliable correlations between improvement in stereopsis and improvement in threshold ratios or amblyopic eye acuity although the trends were positive. Since participants completed a varying number of training blocks (between 2 and 21, mean = 8.2, SD = 6.3) and undertook their training at varying rates (between 0.5 blocks per week and 3.7 blocks per week, mean = 1.9, SD = 1.3) we were able to investigate the relationship between functional improvement and both duration and intensity of training. The intensity of training (i.e. blocks per week) was positively correlated with threshold ratio improvement (Rho[9] = 0.7, $p = 0.04$, Fig. 4C) but not with either stereo or acuity improvement. The number of blocks did not significantly correlate with any of our measures of functional improvement ($p > 0.05$). This suggests that for at least some measures of amblyopic improvement, more intense periods of training (i.e. a high number of blocks per week) may be a most effective training regime.

5. General discussion

In a previous study we describe a new method for quantifying suppression, something that is only done in a binary fashion in the clinic at present. The method is based on a signal/noise approach but applied within the context of dichoptic stimulation. This allowed us to demonstrate for the first time that threshold as well as suprathreshold information can be combined between the eyes of strabismic amblyopes under suitable, albeit artificial, viewing conditions (Baker et al., 2008). Here we show that intensive training using this dichoptic approach leads to a progressive strengthening of binocular vision such that it can eventually operate under natural viewing conditions where the left and right image contrast is equal. We found this to be the case in 8 /9 subjects tested and it should be emphasized that all subjects were adult amblyopes well beyond the accepted "critical period" for patching therapy (Epelbaum et al., 1993). Concurrent with this improvement in the efficacy of binocular combination we also found that the stereopsis of a majority was established and that also the monocular acuity improved. These improvements were significant and in some cases large.

We interpret these findings in terms of the suppressive state that is known to exist in strabismic humans (Jampolsky, 1955, Joosse et al., 1999, Joosse et al., 1997, Travers, 1938, von Noorden, 1985) and in animals made artificially strabismic in early life (Sengpiel and Blakemore, 1996, Sengpiel et al., 1994, Sengpiel et al., 2006). The evidence suggests that suppression renders what is a structural binocular visual system, functionally monocular. For example, animal studies have shown that suppression occurs in the early visual cortex (Sengpiel and Blakemore, 1996) and that it is mediated by GABA (Sengpiel et al., 2006). Furthermore, the apparent loss of binocular cortical cells in strabismic cats can be pharmacologically reversed (Mower et al., 1984) by ionophoretic applications of bicuculline (selective blocker of GABA A receptors), suggesting an active suppression rather than a loss of cellular function. In humans, it has been shown that strabismics exhibit normal binocular summation of contrast signals if the signals are adjusted to take into account the monocular amblyopia (Baker et al., 2007) and that there is normal binocular combination of suprathreshold signals if suppression is accounted for by providing each eye with stimuli of different contrast (Mansouri et al., 2008). It is therefore not that surprising that if suppression is reduced via training that binocular vision, including stereopsis, can be re-instated. A similar case has been put in the case of anisometropic amblyopia for the importance of active anti-suppression training (Wick et al., 1992).Our recent demonstration (Thompson et al., 2008) of improved monocular function in the amblyopic eye after repetitive transcranial magnetic stimulation (rTMS) of the visual cortex in adult strabismics suggests that not all function is lost even in adults. An obvious explanation in terms of the time scale of the improvement demonstrated in the rTMS study (10 min) is that a significant fraction of the monocular loss is due to an active tonic inhibition from the fellow fixing eye even when the fellow fixing eye is closed. If this is the case, then the monocular improvements in acuity that have been shown to occur here, as suppression is reduced, are not unexpected. That the acuity does not return to normal levels suggests that not all of the monocular loss in the adult can be ascribed to suppressive factors. It is also worth noting that in both the current study and our prior rTMS study (Sengpiel and Blakemore, 1996), there was a significant, positive, correlation between the amount of improved monocular function in the amblyopic eye and the depth of amblyopia, i.e. the worse the amblyopic the greater the potential improvement. This demonstrates that sufficient plasticity for supporting improved amblyopic eye function exists especially in the visual cortex of adults with deep amblyopia. The general utility of binocular as opposed to the current monocular (i.e. patching of the fixing eye) viewing has been shown recently in cats monocularly deprived of vision in one eye throughout the critical period (Kind et al., 2002, Mitchell et al., 2001). The visual recovery of function, as assessed by both behavoural and physiological measures, is far better if the cortex receives a correlated binocular input (i.e. with both eyes open) than it is when only one eye is open (i.e. amblyopic eye) and the other occluded (i.e. the fixing eye) (Kind et al., 2002, Mitchell et al., 2001).

The training effect. It is well documented in the suppressive literature of the last century that the more suppression is measured, the more it may diminish in degree (Travers, 1938). In the present approach we have exploited this by establishing an anti-suppression training protocol. Our method allows us to verify what conditions are required for binocular combination in each amblyope and to provide controlled stimulation of an intensive kind under these precise conditions. Most subjects showed improvements after 10,000 trials.

Previous approaches. Previously, it has been demonstrated using monocular perceptual learning techniques that modest though significant improvements in monocular function are possible in adult amblyopes (Li et al., 2005, Polat et al., 2004, Webb et al., 2006). Our study represents a significant departure from these previous studies however, by targeting perceptual training directly at binocular function. Our study also adds further support to the basic principle that functional recovery is possible in adult amblyopes. The training regime that we employ, which entail repeated measurement of psychophysical performance using staircase techniques, is comparable to those used previously for different monocular tasks (e.g. Huang et al., 2008) and is efficient as it maintains the majority of stimulus presentations close to psychophysical threshold.

Although dichoptic approaches to improving vision in amblyopia have been considered before (Cleary et al., 2009), our approach is fundamentally different from these previous studies. Cleary et al. (Cleary et al., 2009), reported results of using a dichoptic driving game in a group of amblyopic children as an alternative to conventional occlusion to promote recovery of vision in the amblyopic eye. It is important to note that in this study there was no attempt to promote binocular combination between the two eyes in terms of balancing the contrast of the stimuli to each eye, as was the case in the present study. They report improvements in monocular acuity for both low contrast and high contrast letters in half of their cohort. This differs from the current report where we report improved binocular function (fusion and stereopsis) as well as monocular acuity. While both approaches use dichoptic methods of stimulation, our approach is different in a number of fundamental ways. For example, since we are primarily interested in binocular vision, suppression is measured and conditions arranged (by manipulating interocular contrast) under which we can psychophysically verify that binocular combination takes place. Training takes place under these controlled conditions of binocular combination. Finally, our stimuli are evenly and randomly distributed across the visual fields of the two eyes while not containing any featural interocular differences.

The initial data reported here suggests that our new approach to improving both binocular and monocular visual function in adult amblyopia is effective in the majority of cases. Furthermore, the effects are most pronounced when the amblyopia is relatively severe and for optimal results an intensive training period is required. These results form the foundation for future studies investigating the precise time course of the effects when training intensity is normalized within the test group and the duration of the beneficial effects after the termination of treatment. Since there are no established treatments for amblyopia in adulthood, it is not possible to use other treatment approaches as a baseline for assessing the effectiveness of our intervention, however a comparison of monocular vs. binocular training using moving dot stimuli would be highly informative. Most importantly however is the application of this new technique to children with amblyopia. Adult amblyopes, as tested in this study, are an important and conservative test case due to the relative lack of plasticity in the adult visual system as compared to the juvenile visual system (Epelbaum et al., 1993). Therefore any treatment that is effective in adulthood should have even more pronounced effects in childhood. Since there are currently few alternatives to the patching/penalization approach to amblyopia treatment commonly used in children, a new non-invasive approach such as the one presented here could be highly beneficial for this patent population.

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