CLINICAL AND EXPERIMENTAL
OPTOMETRY

RESEARCH PAPER

The iPod binocular home-based treatment for amblyopia in adults: efficacy and compliance

Clin Exp Optom 2014; 97: 389–398 DOI:10.1111/cxo.12192

Robert F Hess* DSc
Raiju Jacob Babu† OD
Simon Clavagnier* PhD
Joanna Black§ OD
William Bobier† PhD
Benjamin Thompson§ PhD

* McGill Vision Research, Department of Ophthalmology, McGill University, Montreal, Quebec, Canada
† Department of Optometry and Vision Science, University of Waterloo, Waterloo, Ontario, Canada and § Department of Optometry and Vision Science, University of Auckland, Auckland, New Zealand

Submitted: 5 April 2014
Revised: 17 May 2014
Accepted for publication: 3 June 2014

Background: Occlusion therapy for amblyopia is predicated on the idea that amblyopia is primarily a disorder of monocular vision; however, there is growing evidence that patients with amblyopia have a structurally intact binocular visual system that is rendered functionally monocular due to suppression. Furthermore, we have found that a dichoptic treatment intervention designed to directly target suppression can result in clinically significant improvement in both binocular and monocular visual function in adult patients with amblyopia. The fact that monocular improvement occurs in the absence of any fellow eye occlusion suggests that amblyopia is, in part, due to chronic suppression. Previously the treatment has been administered as a psychophysical task and more recently as a video game that can be played on video goggles or an iPod device equipped with a lenticular screen.
The aim of this case-series study of 14 amblyopes (six strabismics, six anisometropes and two mixed) ages 13 to 50 years was to investigate: 1. whether the portable video game treatment is suitable for at-home use and 2. whether an anaglyphic version of the iPod-based video game, which is more convenient for at-home use, has comparable effects to the lenticular version.
Methods: The dichoptic video game treatment was conducted at home and visual functions assessed before and after treatment.
Results: We found that at-home use for 10 to 30 hours restored simultaneous binocular perception in 13 of 14 cases along with significant improvements in acuity (0.11 ± 0.08 logMAR) and stereopsis (0.6 ± 0.5 log units). Furthermore, the anaglyph and lenticular platforms were equally effective. In addition, the iPod devices were able to record a complete and accurate picture of treatment compliance.
Conclusion: The home-based dichoptic iPod approach represents a viable treatment for adults with amblyopia.

Key words: amblyopia, children's vision, visual acuity

Amblyopia traditionally has been thought of as a monocular disorder that has a binocular consequence. According to this view, the amblyopic visual system is, in some way, 'lazy' or immature and the logical treatment approach is to force use of the amblyopic eye by occluding the fellow sighted eye with a patch. Previously, the patch was worn all day for months or in some cases years.[1] Now we know that less patching, even as little as two hours per day, can be just as effective as all-day patching and can significantly improve visual acuity in the amblyopic eye;[2] however, not all patients respond to patching and of those who do, many have residual amblyopia after treatment is terminated regardless of compliance.[3] More importantly, binocular vision is not automatically restored once the vision in the amblyopic eye has been improved. In fact, more often than not, once the patch is removed after therapy has ended, the amblyopic eye is suppressed by the fellow sighted eye and can, over time, lose some of the gains achieved as a result of the therapy.[4]

There is now evidence to suggest that the traditional view of amblyogenesis may be incorrect. Amblyopia may be the consequence of a primary disruption to binocular vision, in which suppression plays a major part. This idea is not new,[5] it is supported by the direct relationship between suppression and amblyopia that has been reported in animal models,[6] by the restoration of vision in deprived animals[7] as well as clinical studies on adults[8] and children[9] with amblyopia. Furthermore, it has been shown recently that therapy aimed at promoting binocular vision by strengthening fusion and reducing suppression, results in improved vision in the amblyopic eye as well as a recovery of binocular function and stereopsis.[10–12] This treatment was based on psychophysical measurements, which demonstrated that patients with amblyopia exhibited binocular visual function if the image shown to the amblyopic eye had a higher contrast than that shown to the fellow eye.[13] The treatment incorporates a task that requires information to be combined between the two eyes and begins with a patient-specific interocular contrast offset that overcomes suppression and allows for the task to be completed. Over time, binocular function improves and the contrast offset between the two eyes can be reduced until, in many cases, no contrast offset is required. Using this approach, it has been demonstrated recently that, as well as playing a key role in the development of amblyopia, suppression may also actively prevent recovery of visual function by inhibiting visual cortex plasticity.[14]

Although this binocular treatment was initially developed in the laboratory using cumbersome psychophysical equipment, it has been translated recently to a more convenient head-mounted display[14–17] and a hand-held iPod device.[12,18] These stimulus display platforms can be used in a clinical setting and have the potential to be used in the home. We have also developed a video game version of the treatment to make it as enjoyable as possible with the goal of improving compliance and hence treatment outcomes. The combination of the iPod platform and the video game version of the treatment is particularly suitable for use at home. This would meet with the expectations of clinicians and patients, who are used to amblyopia treatment being administered in the home rather than the clinic.

The use of our binocular treatment outside of the clinic setting poses a number of challenges. These include compliance, automatic updating of the interocular contrast difference as binocular function improves and accurate dichoptic presentation of visual stimuli. In the clinic, compliance problems do not occur as patients are monitored and interocular contrast can be adjusted manually, based on session by session evaluation of task performance. In addition, dichoptic presentation can be achieved on the iPod device using a lenticular overlay screen. The advantage of using a lenticular overlay is that the luminance contrast is preserved. The disadvantage is that the device must be precisely aligned with the eyes to reduce crosstalk between the images presented to each eye. In the clinic, this can be achieved using a chinrest and a stand for the iPod; however, this cannot be done easily in the home. In the present study, we assessed the practicality of at-home use of the iPod video game treatment. Patients were required to comply with a treatment schedule, the interocular contrast difference was adjusted automatically based on game performance and patients were responsible for assuring correct alignment of the iPod device equipped with a lenticular screen. We also developed an anaglyph method of dichoptic stimulation to complement our original lenticular approach. This has the advantage that head alignment is no longer necessary; however, red/green glasses have to be worn. We hoped that this approach may be better suited to younger patients. We set out to answer two questions.

1. Is the home-based binocular treatment as effective as its clinic-based counterpart[18] that was conducted under supervision?
2. Is the anaglyphic version as effective as the lenticular version?

METHODS

Concurrent pilot field tests were run at the Department of Ophthalmology McGill University, School of Optometry and Vision Science at University of Waterloo and the Department of Optometry and Vision Science, University of Auckland in New Zealand. The research was carried out following clearance from the Institutional Review boards of each university and adhered to the tenets of the Declaration of Helsinki.

Participants (n = 14; aged 13 to 50 years) who had amblyopia due to anisometropia (difference in refractive error between the two eyes), strabismus (misalignment of the eyes) or both were recruited at the individual testing facilities. The amblyopic participants had a difference of at least two lines between the eyes on a logMAR visual acuity chart and had impaired stereo acuity (greater than 40 arc seconds).

All the participants underwent a standard clinical protocol in all the three pilot testing sites. The clinical examination is detailed below and clinical details provided in Table 1.

Visual acuity

Visual acuity was obtained using a computerised version of the Bailey–Lovie logMAR chart; either the Test Chart 2000 pro and Khyber Vision iPad application or the Medmont computerised visual acuity testing system, model AT20R, (Melbourne, Victoria, Australia). These two tests do not differ from standard chart-based tests when correct lighting conditions are employed.[19] A letter by letter scoring procedure was adopted to obtain visual acuity. A termination criterion of five errors on a line was used.

Stereoacuity

Stereoacuity was measured using the Randot stereofly test or the Randot® Preschool Stereo Acuity test (Stereo Optical Company, Chicago, Illinois, USA). Results were recorded as log threshold. If stereopsis was unmeasurable, a log threshold of four was recorded.

Strabismus

Unilateral and alternate cover tests were used to determine the presence of a tropia (manifest deviation) or phoria (latent deviation) and the observed deviation, if any, was neutralised by the use of a prism of the required magnitude (prism cover test). These were worn only during the treatment. Amblyopic participants were classified as exotropes or esotropes based on the direction of the deviation.

Worth four dot test

The test was performed at both distance (1.6 m) and near (33 cm). The distance measurement was such that the lights subtended one degree of visual angle and the near measurement was such that a six degree visual angle was subtended. The placement of the red-green filters was according to convention: red filter over the right eye and green filter over the left eye. The participants were to report whether they saw all the four lights and report the colour of each. If the participants reported either only two reds or three green coloured lights, they were considered to have complete suppression. If they reported a total of five coloured light, they were considered to have diplopia and if they reported four lights with the bottom light appearing either red or green then they were considered to have partial suppression.

Bagolini striated lens test

Suppression by the participants was also assessed qualitatively using the Bagolini striated lens test, which is considered to have a less dissociating effect than the Worth four dot test. Participants viewed a light source at two test distances (distance 1.0 m and near 33 cm), while wearing the striated glass lenses oriented at 45 and 135 degrees over their habitual spectacle or contact lens correction. In the instance of normal binocular vision, the participants would report an X corresponding to '/' seen by one eye and '\' seen by the other eye. In the case of complete suppression, the participants would perceive only one of the two lines that form an X. In the case of a central suppression scotoma, the percept would be of a cross with one line having a missing region close to the fixation light. In theory the size of the suppression

Observer	Age/sex	Type	Refraction	Visual acuity	Stereo (RDS) and suppression	History
SB (L)	22/M	Anisometrope	RE: +3.00 D/-0.50 x 90 LE: +1.00 DS	RE:+0.14 [20/27^{+2}] (6/7.5^{+2}) LE: -0.1 [20/16] (6/4.8)	800 arc secs (RDS) W4D: Partial suppression Bagolini: Fusion DOTS: 34.4 FFE contrast, AME/FFE = 3.59	Detected at age 12 years No patching
MS (L)	41/F	Anisometrope	RE: -1.5 DS LE: +3.00/-1.5 x 145	RE: -0.1 [20/16] (6/4.8) LE:+0.36 [20/40^{+3}] (6/12^{+3})	400 arc sec W4D: Fusion at near, suppression at distance Bagolini: Fusion with central suppression DOTS: 12.6 FFE contrast AME/FFE = 5.95	Detected at age 5. Patching 2 to 3 hours/day for 1 year.
SJ (L)	50/M	Microtrope (4 prism BO test)	RE: +1.75 DS LE: +1.75/-1.00 x 165	RE: +0.5 [20/63] (6/18) LE: 0.0 [20/20] (6/6)	Stereo: < 800arc sec W4D: Fusion with partial suppression Bagolini: Fusion with occasional suppression DOTS: 31 FFE contrast AME/FFE = 2.17	Detected at age 5, Patching—did not comply.
SA (L)	29/M	Mixed Left esotropia 6 PD	RE: -2.50/ -1.25 x 180 LE: + 0.50/-1.50 x 180.	RE: -0.1 [20/16] (6/4.8) LE: +0.36 [20/40^{+3}] (6/12^{+3})	Stereo: < 800arc sec W4D: Fusion (distance and near) Bagolini: Fusion DOTS: 28.6 FFE contrast AME/FFE = 3.14	Detected at age 5. History of strabismus surgery at age 5. Patching 1 hour/day for 6 months.
PS	28/M	No squint Considered as strabismus on account of history (30 PD corrected at age 5)	RE: +1.50/-0.50 X 12 LE: +3.50/-2.00 x 160	RE: -0.26 [20/12.5^{-3}] (6/3.8^{-3}) LE: +0.28 [20/40^{-1}] (6/12^{-1})	Stereo: < 800arc sec W4D: Diplopia (distance) Fusion with intermittent suppression (near) Bagolini: central scotoma left eye (distance and near) DOTS: 31.2 FFE contrast AME/FFE = 5.46	History of strabismus surgery at age 5 (left esotropia 30 PD) Patching for 1 year 2-3 hours/day
MT	40/M	Strabismus: Right esotropia 6 PD	RE: -2.75/-1.00 x 105 LE: -2.75/-1.00 x 80	RE: +0.34 [20/40^{-2}] (6/12^{-2}) LE: -0.12 [20/16^{-1}] (6/4.8^{-2})	Stereo: < 800arc sec W4D: Intermittent suppression (distance) Fusion (near) Bagolini: RE central scotoma (distance and near) DOTS: 38.8 FFE contrast AME/FFE = 4.42	Detected at age 6 Patching for more than 8 hours a day for more than a year.
ST	24/F	Strabismus: Right exotropia 8 PD	RE: -2.75/-0.75 x 25 LE: -3.25/-1.25 x 10	RE: +0.56 [20/80^{-2}] (6/24^{-2}) LE:-0.1 [20/16] (6/4.8^{-2})	Stereo: 400 arc sec W4D: Fusion (distance and near) Bagolini: Intermittent suppression DOTS: 15.1 FFE contrast AME/FFE = 8.51	Detected at 8 years Patching for 6 hours or more for 1 year.
XU	39/M	Strabismus: Right esotropia 10 PD	RE: +6.75/-2.50 x 30 LE: +5.00/-1.75 x 162	RE: +0.3 [20/40] (6/12) LE: -0.1 [20/16] (6/4.8^{-1})	Stereo: < 800arc sec W4D: Suppression RE (distance); fusion (near) Bagolini: RE central suppression (distance and near) DOTS: 38.4 FFE contrast AME/FFE = 2.57	Detected at age 4 Patching for 1 year for 8 hours/day. History of strabismus surgery at age 4 for both eyes.
OT	22/M	Strabismus: left esotropia 4 PD	RE: -1.00 DS LE: -1.00/-0.25 x 160	RE: -0.1 [20/16] (6/4.8) LE: +0.3 [20/40] (6/12)	400 arc sec W4D: Fusion Bagolini: central scotoma at distance; fusion (near) DOTS: 38.8 FFE contrast AME/FFE = 2.57	Detected 12+ years No patching
AS	46/M	Mixed left esotropia 8°	RE: plano LE: -4.00 /-1.75 x 40	RE: -0.1 [20/16] (6/4.8) LE: +0.3 [20/40] (6/12)	Stereo: 400 arc sec W4D: Intermittent suppression (distance) Fusion (near) Bagolini: LE central scotoma	Detected at age 27 No patching No surgery
DD	24/M	Anisometrope	RE: + 0.25/-0.25 x 175 LE: +1.75/-2.25 x 12	RE:-0.1 [20/16] (6/4.8) LE: 0.26 [20/32^{+3}] (6/9.5^{+3})	Stereo: 400 arc sec W4D: Intermittent suppression (distance) Fusion (near) Bagolini: Fusion	Detected at age 24 No patching No surgery
NDA	49/F	Anisometropic	RE: +1.25 DS/-0.25 x 175 LE: +5.00 DS/-0.50 x 180	RE: 0.2 [20/32] (6/9.5) LE: 0.53 [20/63] (6/19)	No stereo W4D: left eye suppression at both distance and near Bagolini: LE central suppression	Detected in childhood (uncertain of age) No patching Only wearing near correction habitually
YZ	32/F	Anisometrope	RE: +1.00/-0.25 x 105 LE: +3.50 DS	RE: 0.0 [20/20] (6/6) LE: 0.4 [20/50] (6/15)	Stereo: 200 arc sec W4D: Fusion Bagolini: Fusion	Detected in childhood (uncertain of age) No patching and a brief period of atropine penalisation
EL	13/M	Anisometropic	RE: +1.25/-0.25 x 10 LE: +6.00/-2.00 x 10	RE: -0.2 [20/12.5] (6/3.8) LE: 0.3 [20/40] (6/12)	Stereo: 63 arc sec W4D: Left eye suppression distance, fusion at near Bagolini: Intermittant suppression	Detection at age 11 No patching, optical correction only

RE: right eye, LE: left eye, RDS: Randotdot stereogram, W4D: Worth 4 Dot test, F: female, M: male, AME: Amblyopic eye, FFE: fellow fixing eye, BO: base out, DS: dioptre sphere, DC: dioptre cylinder, PD: prism dioptres, L: lenticular iPod training used.

Table 1. Clinical details of amblyopic observers participating in the iPod training study

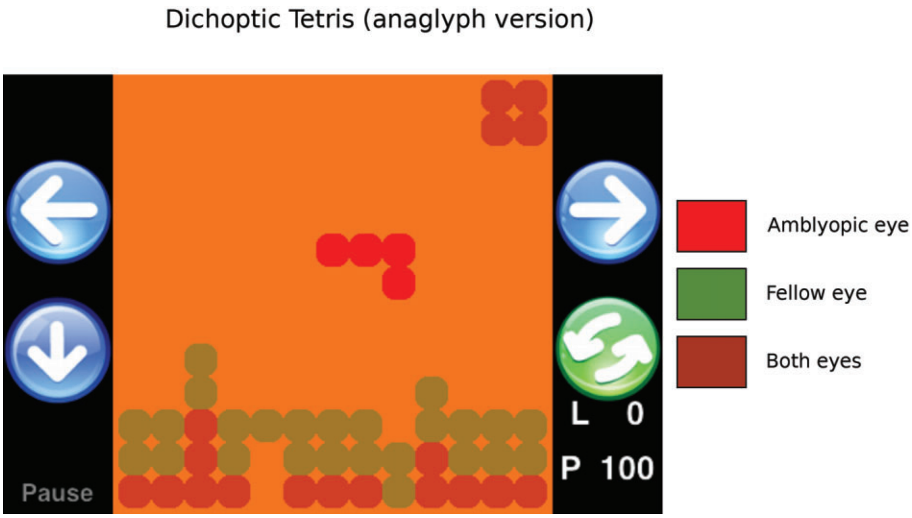

Figure 1. The anaglyphic version of the iPod-based Tetris game. The high-contrast red blocks were seen by the amblyopic eye. These were the falling blocks. The low-contrast green blocks were seen by the fellow fixing eye (FFE). These were the superficial ground plane blocks relevant to the task. Some ground plane blocks were seen by both eyes (brown/orange). Over time and successful play, the contrast offset between the eyes was reduced (the fixing eye contrast was increased by 10 per cent of its starting value every 24 hours). We identified two phases of fusional recovery (Figures 7A and B); phase 1 where the contrast is automatically incrementing in the fixing eye with successful game play and phase 2 where the contrast in the FFE has reached an asymptote (usually 100 per cent), which is the same as that of the fellow amblyopic eye.

scotoma determines whether this percept is seen at both distance and near. In particular, if the scotoma is seen only at distance then a smaller scotoma (approximately one degree) is assumed.

Objective quantification of suppression

We quantified the amount of suppression using the dichtopic global motion test.[13,15,17] This test involves the presentation of signal elements to one eye, noise elements to the other eye and a variable interocular contrast offset. Suppression is measured by identifying the contrast offset between the two eyes that is required for normal binocular combination of the signal and noise elements, whereby lower contrast elements are shown to the fellow eye. Following previously published protocols, stimuli were presented using a MacBook Pro laptop computer running Matlab (Mathworks Ltd, Cambridge UK) and Psychophysics Toolbox, Version 3.[20] The stimuli were displayed using a Z800 duel pro headmounted display (eMagin Corporation, New York, NY, USA). This headmounted display model contains two OLED screens, one for each eye. The screens have a high luminance, a linear luminance response profile and refresh simultaneously at 60 Hz, therefore avoiding motion smear. The device also allows for different stimuli to be presented to each eye. To achieve this, each frame of the dichoptic stimulus was computed as a single image with a resolution of 600 by 1600 pixels. A Matrox Duel Head2Go external video board was then used to split each frame between the two headmounted display screens at a resolution of 600 by 800 pixels per screen. A photometer (United Detector Technology, San Diego) was used to ensure equal luminance of the two screens and to confirm a linear luminance response.

Stimuli were random dot kinematograms based on those used by Mansouri, Thompson and Hess[13] and were presented within a stimulus aperture with a diameter of 22 degrees. One hundred dots (with dot luminance modulation varied according to $\frac{(L_{dots} - L_{background})}{(L_{dots} + L_{background})}$) were displayed upon a mean luminance background of 35 cd/m^2. Each dot had a radius of 0.5 degrees° and moved at six degrees per second. The dots had a limited lifetime whereby on any single frame, each dot had a five per cent chance of disappearing and being redrawn in a new spatial position. To avoid interaction of the stimulus dots with the central dark fixation dot (radius 0.35 degrees), stimulus dots did not enter the central region of the display aperture (radius 2 degrees). Dots that passed through this central region disappeared and were redrawn on the opposite side of the central area with the appropriate temporal delay to maintain a constant speed. When stimulus dots reached the edge of the display aperture, they were wrapped around. Stimuli were shown for one second.

Refraction

Refraction was performed, if participants were not habitually wearing any correction or if they had not visited their eye-care practitioner for more than two years. If a new prescription was required participants completed a refractive adaptation period that ended when two consecutive visual acuity measurements made a minimum of four weeks apart indicated stable visual acuity (less than 0.1 logMAR difference in the two measurements). Participants (strabismic as well as anisometropic) were asked to wear their correction full-time during the refractive adaptation period.

Training regimen

The training was completed using an iPod touch device using the popular Tetris game.[18] The advantages of using the Tetris game were that most players have played the game before, it is a very simple game to learn and the game configuration lends itself to our dichoptic treatment principle, as it includes multiple distributed elements. The players have to align various falling elementary shapes that appear randomly on the top of the screen. Players have to interact continuously with the falling blocks by changing the position and orientation of the falling block shapes to form tessellated rows of blocks at the bottom of the screen. Dichoptic presentation of the blocks can be achieved using either a lenticular screen [18] or an anaglyph presentation. Here, we illustrate the anaglyphic version (Figure 1). The falling blocks can only be seen by the amblyopic eye (Figure 1, red blocks). The blocks forming rows at the bottom of the screen are seen only by the fellow fixing eye (Figure 1, green blocks). The ground

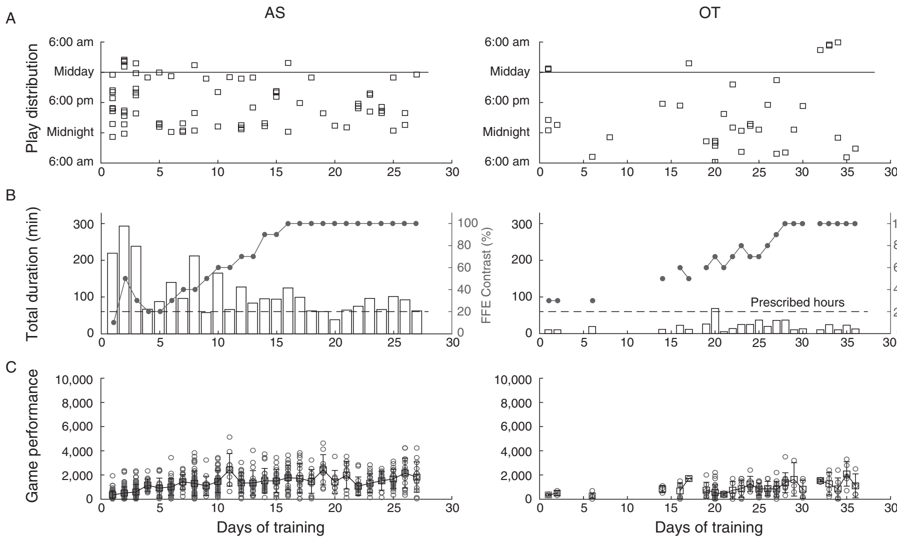

Figure 2. Graphical representation of information contained in the iPod's log file after the home-based treatment for two patients (AS and OT). In row A, the distribution of game play over a 24-hour period is shown. In row B, the total duration of game play each day is shown (left, Y-axis) as well as how the contrast changed (right, Y-axis), as a consequence of game performance (row C). Each data point represents an individual game. See main text for further details.

plane blocks that are not relevant to the score are seen by both eyes (brown/orange blocks). At the start of training, blocks were presented to the amblyopic eye at a higher contrast than the blocks presented to the fellow eye to overcome suppression and allow for binocular combination.[13,15] The contrast offset was determined separately for each participant, based on the results of the suppression measurements made using the dichtopic global motion test.

RESULTS

The treatment is based on the finding that if the contrast is reduced in the fellow sighted eye, depending on the severity of suppression, there will be a value for which the information is combined by the fellow sighted and amblyopic eyes.[10–12] Over time this reduced contrast can be slowly increased while binocular combination is maintained. We use a video game,[18] in which different elements are seen by fellow sighted and amblyopic eyes and the combination of these elements is essential to score in the game, hence it can only be done binocularly. The elements seen by the fellow sighted eye are reduced in contrast until the game can be successfully played (when a player goes up one level by clearing four lines, the game gets faster and contrast is incremented but just once in a 24 hour period) and gradually increased each and every day that the game is successfully played. The contrast of elements seen by the fellow sighted eye is automatically increased, if the game is played successfully and this is an indication that suppression from the fellow sighted eye is reducing. Once the game can be successfully played with the same contrast in both eyes, suppression has been eliminated and binocular vision in its most rudimentary form, (fusion) has been re-instated. The game is played on an iPod device and information about exactly how the contrast is changed, how frequently the game is played, when during the day it was played and how successfully it was played is contained in the iPod's stored log files.

Figure 2 shows two examples of information derived from iPod log files for a 30 to 40 day period of home-based therapy. The middle graph (B) in each case reflects how the contrast of stimuli presented to the fellow fixing eye (FFE) changed as a function of duration of video game play (grey circles). The contrast of the blocks presented to the amblyopic eye was fixed at 100 per cent. At the start of training, low contrast stimuli had to be presented to the fellow eye to allow for binocular combination (verified by successful game play). As training progressed, higher contrasts could be tolerated in the fellow eye until, by the end of training, no interocular contrast difference was needed. This progressive change in the interocular contrast required for binocular combination indicates a weakening of the suppressive influence of the fellow eye over the amblyopic eye. Once the fellow eye can be given stimuli of the same contrast as that seen by the amblyopic eye, suppression has been eliminated. Typically, this is what happens over the treatment period. The rate at which contrast changes is determined by the algorithm we used (10 per cent change per 24 hours, if the game is played successfully) and also by individual variation, depending on the severity of suppression. The top graph (A) in Figure 2 shows how the treatment was distributed over a 24-hour period. In these two cases, the compliance for patient AS is excellent but initially (up till day 15) patient OT exhibits poor compliance. The rate of improvement in the contrast tolerated by the fixing eye (grey circles in B) reflects this; in OT's case the contrast improvement is delayed by 15 days. The bottom graph (C) shows how the game performance varied across the treatment period. Game performance needs to be consistent and above a threshold level for the contrast to be automatically changed every 24 hours. In these two cases, game performance meets these criteria, although for OT game performance is poor in the first 15 days most likely due to inadequate playtime.

Figure 3 shows that the contrast tolerated by the fellow sighted eye at the end of the treatment period (the contrast asymptote) increased in all patients and that this was as true for both anaglyphic (unfilled symbols) and lenticular (filled symbols) platforms. The averaged pre-treatment contrast was 29 per cent and the average post-treatment contrast was 97 per cent (indicated by the solid grey diamond in Figure 3). Contrast has to be reduced for the fellow eye because of suppression and therefore, an increase in the contrast tolerated by the fellow eye indicates the extent to which dichoptic game play was successful in reducing suppression and re-instating binocular combination in its simplest form. The form of this increased tolerance to the contrast of stimuli shown to the fellow eye is shown in the data depicted in Figure 2 (grey dotted curve in B). The results in Figure 3 show that

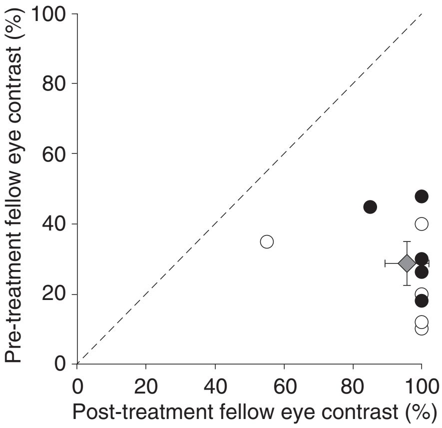

Figure 3. Comparison of the contrast that the fellow eye could tolerate while still maintaining dichoptic game play before and after the iPod home-based treatment. Results falling on the unity line indicate no change, results falling below the unity line indicate an increase in contrast which signifies a decrease in suppression. Results obtained for the lenticular (filled symbols) screen and the anaglyphic (unfilled symbols) screen are displayed separately. The average pre- and post-treatment contrast is indicated by the solid grey diamond with its associated 95 per cent confidence intervals.

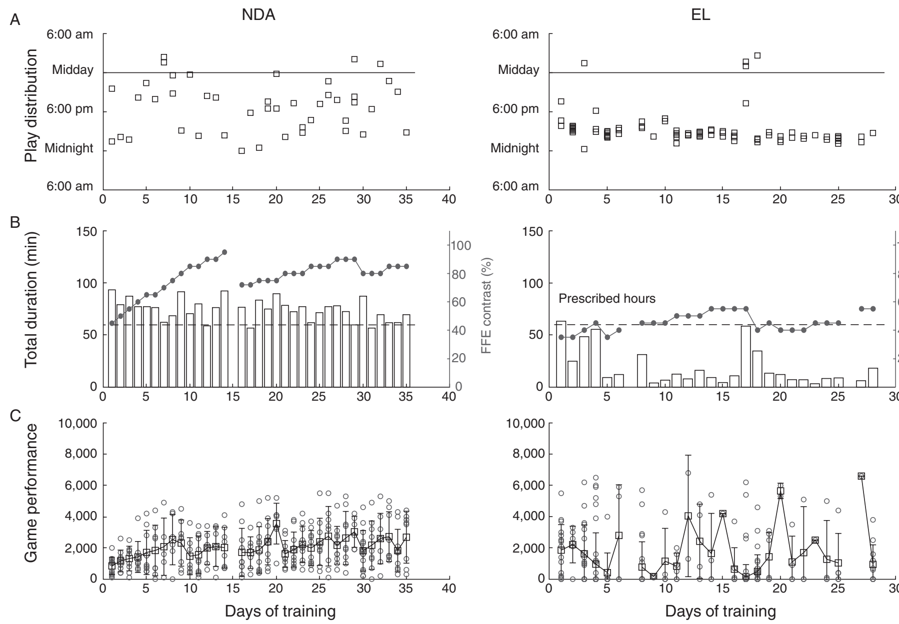

Figure 4. Graphical representation of information contained in the iPod's log files after the home-based treatment for two patients, whose contrast results in Figure 3 represent outliers (NDA and EL). In A, the distribution of game play over a 24-hour period is shown. In B, the total duration played each day is shown (left, Y-axis) as well as how the contrast of elements presented to the fellow eye changed (right, Y-axis) as a consequence of performance (C). Each data point represents an individual game.

all but two patients had their suppression eliminated and their binocular combination re-instated.

The two outliers

The log files for these two patients whose contrast did not reach 100 per cent are displayed in Figure 4.

Patient NDA's log file shows an initial strong increase in contrast reaching 100 per cent (B), associated with good game performance (C) and excellent compliance (A). At the early stage, when this patient was treated, the automatic contrast adjustment was not in operation and the contrast was increased manually on daily clinic visits, if the performance was good. On day 15, NDA complained of asthenopia and the contrast was reset to 70 per cent during a clinical visit and then, through successful game play, gradually, manually increased again to 90 per cent but manually reset to 82 per cent because of continuing asthenopia. This subject could achieve 100 per cent visually but it was associated with discomfort. On the basis of the log file alone, this patient benefited from training in that suppression has been reduced to a very low level. Stereoscopic vision improved from no stereopsis pre-treatment to coarse stereopsis (800 arc seconds) post-treatment. Acuity improved from 0.53 logMAR pre-treatment to 0.36 logMAR post-treatment. Furthermore, as NDA wore a habitual near correction for playing the iPod device, near visual acuity was also measured pre- and post-training for this patient using the Bailey–Lovie near word chart. Near visual acuity improved from N15 to N5 for the amblyopic eye, while near visual acuity remained stable at N3 for the fellow eye. Patient EL's log file shows that there was a great degree of variability in performance (game scores) oscillating from successful play to failure (C). One possible reason for this is seen in the results in B; the game was never played for very long (B), well below that prescribed (horizontal dotted line in the top graph). EL appears to peak at 55 per cent contrast at a number of points during the training period (days 15 to 18, 28 to 29) suggesting that, for the limited time the game was played, the anti-suppression therapy was unable to reduce the depth of his suppression beyond this point in the four-week period. This patient had good stereopsis to begin with (63 arc seconds) and after treatment, it improved marginally to 40 arc seconds. Acuity improved from 0.44 logMAR, pre-treatment to only 0.32 logMAR after treatment. Even though EL was the youngest patient, the age *per se* probably was not the important factor, as it has been shown that if compliance is good, significant gains in contrast can be achieved in the paediatric population.[21,22]

The improvements in stereopsis resulting from the home-based treatment are shown in Figure 5, where stereoscopic performance before and after treatment is plotted such that results falling below the diagonal line indicate decrements in performance, those on the diagonal line, no change in performance and those above the diagonal line, improvements in performance. The mean values for pre- and post-training across all participants are indicated by the solid black symbol with associated 95 per cent confidence intervals. Results for lenticular (filled symbols) and anaglyphic (unfilled symbols) platforms are displayed separately. On average, stereoacuity improved by 0.61 log units in the present study with a mean before treatment of 3.14 (1388 seconds) and after treatment of 2.54 (344 seconds), t(13) = 5.0, p < 0.001. In some cases, stereopsis was not measurable before treatment and was re-established as a result of treatment to fine or coarse levels. The unfilled diamond represents the corresponding pre- and post-treatment average for the same treatment principle (including both Tetris and global motion stimuli) supervised within the clinic (Figure 3). The improvement in stereoscopic acuity from at-home treatment was slightly less than that found previously for the in-clinic treatment. There were no obvious differences in outcome for the lenticular (filled symbols) and anaglyphic (unfilled symbols) platforms for the at-home treatment.

The visual acuity of the amblyopic eye before and after at-home treatment is presented in Figure 6. Results falling above the diagonal unity line indicate improved amblyopic eye acuity. The average pre- and post-treatment acuity is indicated by the solid grey diamond with its associated 95 per cent confidence intervals. The unfilled diamond represents the average pre- and post-treatment acuity of the same treatment supervised within the clinic. On average, the change in logMAR acuity was significant (mean pre-treatment = 0.36, post-treatment 0.25, t[13] = 5.2, p < 0.001), with no obvious difference for lenticular (filled symbols) and anaglyphic (unfilled symbols) platforms. Two patients achieved visual acuity improvements of 0.2 logMAR or better (patients AS and PS). The mean improvement was less than that found previously for the in-clinic treatment. Note that the severity range of this at-home sample (Figure 6) was much less than that of our previous in-clinic sample, (0.6 logMAR compared with 1.2 logMAR).[2]

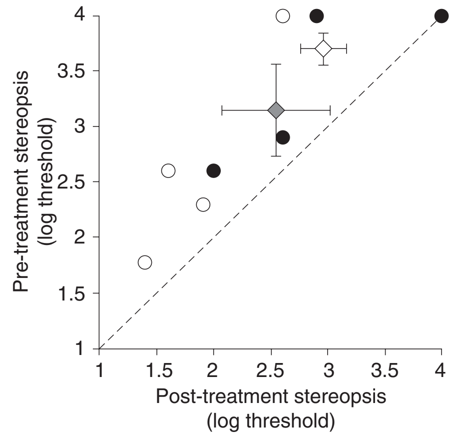

Figure 5. Comparison of stereoacuity before and after the iPod home-based treatment. Results falling on the sloping diagonal line indicate no change, results falling above the unity line indicate an improvement. Results are displayed separately for the lenticular screen (filled symbols) and the anaglyphic (unfilled symbols) screen. The average pre- and post-treatment stereopsis is indicated by the solid grey diamond with its associated 95 per cent confidence intervals. The unfilled diamond refers to the average pre- and post-treatment acuity of the same treatment supervised within the clinic.[23] Three patients (two lenticular, one anaglyphic) had no measurable stereopsis before and after treatment (the data points overlap in the top right of the figure). A number of data points overlap due to the categorical nature of the stereotest. Two participants improved from no measurable stereopsis to 800 arc seconds (4.0 to 2.9 log units), three improved from 400 to 100 arc seconds (2.6 to 2.0 log units) and two improved from 400 to 40 arc seconds (2.6 to 1.6 log units).

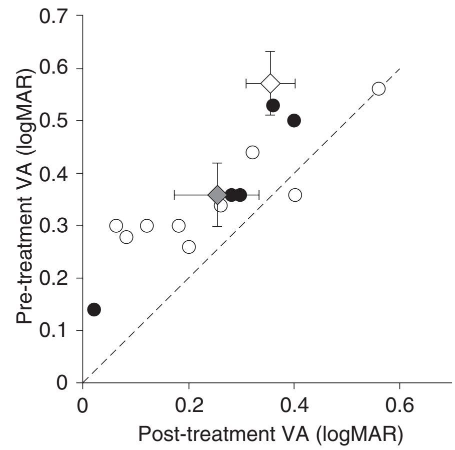

Figure 6. Comparison of visual acuity (logMAR) before and after the iPod home-based treatment. Results falling on the diagonal unity line indicate no change, results falling above the unity line indicate an improvement. Results obtained for the lenticular (filled symbols) screen and anaglyphic (unfilled symbols) screens are displayed separately. The average pre- and post-treatment acuity is indicated by the solid grey diamond with its associated 95 per cent confidence intervals. The unfilled diamond refers to the average pre- and post-treatment acuity of the same treatment supervised within the clinic.[23]

The comparisons with previous work described above include results achieved using a range of different types of displays. To test for any differences in treatment outcome for the iPod device, when used at home versus in the clinic, we compared the results of this study to those reported by Hess and colleagues,[23] who treated patients in the clinic using the lenticular version of the iPod. There was no significant difference between the two datasets. The average improvement in stereopsis across a

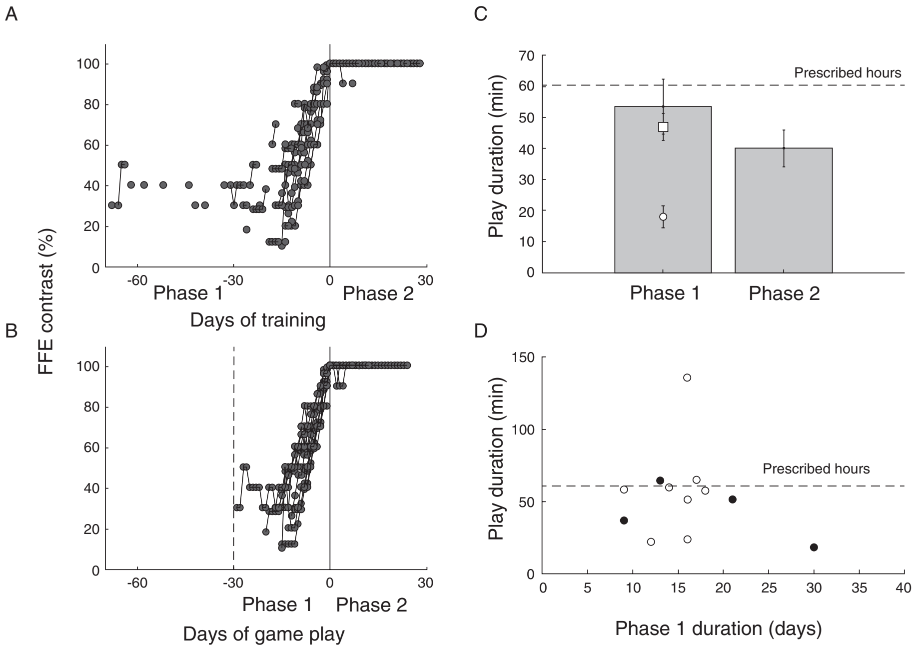

Figure 7. Compliance data for the at-home iPod study. In A, contrast improvements as a function of consecutive days during the treatment period with all the functions aligned to the time corresponding to 100 per cent contrast. In B, same as in A except plotted as a function of the days of consecutive game play (removal of days where the game was not played). In C, the averaged compliance in terms of play duration in minutes for phase 1 and phase 2 (see A and B). The unfilled data points correspond to the individual results of the two outliers discussed in Figure 4 (large symbol—ADL; smaller symbol—EL). In D, individual compliance data show the range of individual variation. The filled symbols are for the lenticular platform and the open symbols for the anaglyphic platform.

number of studies using our previous clinic-based approach[23] was 0.78 ± 0.74 log units of seconds of arc, which was not significantly different from the 0.6 ± 0.5 log units improvement found in the current study (p = 0.36). Similarly, for monocular acuity, the previous clinic-based protocol[23] had resulted in improvements of 0.19 ± 0.17 logMAR, which was not statistically different from the 0.11 ± 0.08 logMAR improvement found in the present study (p = 0.67). The contrast improvements were also similar between studies, with six of 10 (60 per cent) reaching 100 per cent in the fellow eye as compared with 12 of 14 (86 per cent) in the present study. Comparison of the lenticular and anaglyphic platforms in the present study also indicated no significant differences for acuity (0.11 ± 0.05 logMAR versus 0.10 ± 0.09 logMAR), stereopsis (0.56 ± 0.50 log units versus 0.56 ± 0.45 log units) or contrast (75 per cent success versus 90 per cent success), respectively. These findings suggest that home-based outcomes are as good as previously reported clinic-based outcomes[23] and that the anaglyphic platform was just as effective as the previous lenticular platform.

An analysis of the iPod log files also allowed at-home treatment compliance to be assessed. Participants were asked to play for one hour per day for periods of time that ranged between 22 and 108 days. Figure 7 shows a summary of the log file data for all participants who reached 100 per cent contrast in their fixing eye as a result of treatment (13 of 14). In A, contrast improvement as a function of the number of consecutive days within the training period is shown. With the exception of the initial plateau in the results for patient SJ (due to insufficient play time), all the subjects show a similar change in contrast, suggesting an effective treatment duration of 30 days (phase 1). The results shown in Figure 7B are for consecutive days in which the game is actually played (with the days in which there was no play removed). The results are similar in A and B apart from a delay that is evident in A, suggesting that consecutive training days are not a requirement, if days are missed the only consequence is the need for a longer treatment duration. In C, the compliance is shown in terms of play duration/day in minutes. The horizontal dotted line is the prescribed one hour per day and the averaged results in terms of phase 1 training (Figure 7A and B) are not statistically different from that. The two data points superimposed on this bar figure represent the individual results for the two outliers (NDA—small symbol and EL—larger symbol) previously described in Figure 4. Note that once the contrast asymptote is obtained (phase 2), play time significantly decreases. The individual results for compliance are seen in D and there is considerable variability with nine of 14 achieving close to the expected levels or above expected levels and four of 14 achieving lower than expected levels (less than 50 minutes per day).

DISCUSSION

We set out to answer two questions.

1. Is the home-based binocular treatment as effective as the supervised clinic-based treatment?[23]
2. Is the anaglyphic platform for dichoptic stimulation as successful as the previous lenticular platform? The findings of this study suggest that home-based outcomes are as good as previously reported clinic-based outcomes[23] and that the anaglyphic platform is just as effective as the previous lenticular platform.

There are two important differences between treatment that is supervised in the clinic compared with that done at home. First, the viewing conditions, in particular the alignment for the lenticular screen, may not be optimal during treatment and second, the degree of compliance may be reduced at home. Both of these may lead to poorer outcomes for any home-based treatment. Two findings argue that the alignment of the lenticular display is well maintained for the home-based treatment. First, similar results were found between the clinic[23] and home-based protocols and we had gone to some trouble (iPod fixed, remote key controller and chin and forehead rest) to ensure optimal alignment (important to ensure independent images to each eye) was maintained in our previous clinic-based protocol.[23] Second, the anaglyphic version does not require a fixed head alignment and we found comparable results in the present study between lenticular and anaglyphic platforms.

Compliance with the treatment of amblyopia has always been an important issue[24] and we wanted to assess the degree of compliance for our home-based treatment. Information obtained from the log files similar to that illustrated in Figure 2 revealed the following information. In phase 1 of the contrast recovery (Figure 7A and B) there was no statistical difference between treatment duration prescribed and achieved (Figure 7C). In phase 2 of the contrast recovery (Figure 7A and B), compliance was reduced for the group as a whole to about 60 per cent (Figure 7C). There is a considerable degree of variability in compliance within the group with a small subset of patients (four of 14) only playing the game for approximately half that prescribed (Figure 7D). We found no correlation between the visual outcome and the way in which the game time was distributed so long as 30 minutes to one hour per day of game play was achieved.

This new approach to treatment aims to restore binocular vision as a first step, something that is often not achieved after the conclusion of the conventional occlusion therapy, even if the degree of amblyopia has been reduced.[4] Furthermore, we are doing this in adults for whom there is no current therapy. We achieved restoration of simultaneous binocular perception in 12 out of the 14 patients studied (Figure 3). There were no reports of diplopia consistent with our previous studies[10–12,18] and those of others.[16,25] There were significant gains in stereopsis (Figure 5) and amblyopic eye acuity (Figure 6). We conclude that this binocular approach, which targets re-establishing binocular function and improving visual acuity in the amblyopic eye of adult amblyopes can be successfully implemented using either a lenticular or anaglyphic version. This facilitates its application to the paediatric population as the latter approach does not require precise head-to-iPod alignment.[21,22] We also show comparable results for at-home compared with in-clinic use, making it a more convenient treatment option. Finally, the associated log files provide a complete record of compliance in terms of not only how many hours the game was played each day but also how this game play was distributed throughout the day and how successful the patient was at playing the game. We did not find any statistical difference between the training prescribed and that actually carried out at home for the group as a whole and we found no strong relationship between how the game play was distributed throughout the day and the visual outcome, making the treatment tolerant to individual differences in life style. For example, many patients distributed their game play over periods shorter than one hour and this seems not to have affected their treatment outcome, so long as a one hour daily average was maintained. In some cases, treatment was not done on consecutive days and this resulted in a delayed rather than a reduced outcome. The choice of the 10 per cent step in the automatic contrast adjustment was not seen to limit the speed of recovery and we conclude it was conservatively set.

Comparison with alternate methods

At present, there is no generally accepted treatment for amblyopia in adults, as patching has been shown to be less effective for patients above 13 years[26] and would have significant compliance issues. Perceptual learning approaches have been applied and have shown promising results that, like our binocular treatment approach, are independent of age and type of amblyopia.[27,28] Perceptual learning studies have focused on monocular function with training conducted during periods of patching. It is also notable that the vast majority of previously published scientific studies in this area, including our own, have treated participants in the laboratory or clinic setting. The use of a home-based approach, as described here, is an important step forward as it not only aligns the binocular treatment approach with current treatments for amblyopia, such as patching and refractive correction, which all occur in the home, but also allows, for the first time, remote internet monitoring of treatment between office visits.

ACKNOWLEDGEMENTS

This work was supported by a CIHR grant to Professor Hess (#53346) and a University of Auckland Faculty Development Research Fund grant and an HRC grant to Benjamin Thompson.

The binocular treatment described is patented by McGill University and licensed to Amblyotech (www.amblyotech.com). Robert F Hess and Benjamin Thompson are named inventors.

REFERENCES

1. Loudon SE, Simonsz HJ. The history of the treatment of amblyopia. *Strabismus* 2005; 13: 93–106.
2. Repka MX, Beck RW, Holmes JM, Birch EE, Chandler DL, Cotter SA, Hertle RW et al. A randomized trial of patching regimens for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2003; 121: 603–611.
3. Repka MX, Wallace DK, Beck RW, Kraker RT, Birch EE, Cotter SA, Donahue S et al. Two-year follow-up of a 6-month randomized trial of atropine vs patching for treatment of moderate amblyopia in children. *Arch Ophthalmol* 2005; 123: 149–157.
4. Birch EE. Amblyopia and binocular vision. *Prog Retin Eye Res* 2012; 33: 67–84.
5. Wiesel TN, Hubel DH. Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *J Neurophysiol* 1965; 28: 1029–1040.
6. Bi H, Zhang B, Tao X, Harwerth RS, Smith EL 3rd, Chino YM. Neuronal responses in visual area V2 (V2) of macaque monkeys with strabismic amblyopia. *Cerebral Cortex* 2011; 21: 2033–2045.
7. Mitchell DE, Duffy KR. The case from animal studies for balanced binocular treatment strategies for human amblyopia. *Ophthalmic Physiol Opt* 2014; 34: 129–145.
8. Li J, Thompson B, Lam CSY, Deng D, Chan LY, Machara G, Woo GC et al. The role of suppression in amblyopia. *Invest Ophthalmol Vis Sci* 2011; 52: 4169–4176.
9. Narasimhan S, Harrison ER, Giaschi DE. Quantitative measurement of interocular suppression in children with amblyopia. *Vision Res* 2012; 66: 1–10.
10. Hess RF, Mansouri B, Thompson B. A new binocular approach to the treatment of Amblyopia in adults well beyond the critical period of visual development. *Restorat Neurol Neurosci* 2010; 28: 793–802.
11. Hess RF, Mansouri B, Thompson B. A binocular approach to treating amblyopia: anti-suppression therapy. *Optom Vis Sci* 2010; 87: 697–704.
12. Hess RF, Mansouri B, Thompson B. Restoration of binocular vision in amblyopia. *Strabismus* 2011; 19: 110–118.
13. Mansouri B, Thompson B, Hess RF. Measurement of suprathreshold binocular interactions in amblyopia. *Vision Res* 2008; 48: 2775–2784.
14. Li J, Thompson B, Deng D, Chan LY, Yu M, Hess RF. Dichoptic training enables the adult amblyopic brain to learn. *Curr Biol* 2013; 23: R308–R309.
15. Black J, Maehara G, Thompson B, Hess RF. A compact clinical instrument for quantifying suppression. *Optom Vis Sci* 2011; 88: 334–342.
16. Knox PJ, Simmers AJ, Gray LS, Cleary M. An exploratory study: prolonged periods of binocular stimulation can provide an effective treatment for childhood amblyopia. *Invest Ophthamol Vis Sci* 2012; 53: 817–824.
17. Black JM, Hess RF, Cooperstock JR, To L, Thompson B. The measurement and treatment of suppression in amblyopia. *J Vis Exp* 2012; 70: e3927.
18. To L, Thompson B, Blum J, Maehara G, Hess RF, Cooperstock J. A game platform for treatment of amblyopia. *IEEE Trans Neural Syst Rehabil Eng* 2011; 19: 280–289.
19. Black JM, Jacobs RJ, Phillips G, Chen L, Tan E, Tran A, Thompson B. An assessment of the iPad as a testing platform for distance visual acuity in adults. *BMJ Open* 2013; 3: e002730.

20. Brainard DH. The psychophysics toolbox. *Spat Vis* 1997; 10: 433–436.
21. Li S, Subramanian V, To L, Jost RM, Jost S, Stager D Jr, Dao L et al. Binocular iPad treatment for amblyopia. *Invest Ophthalmol Vis Sci* 2013; 54: E-Abstract 4981.
22. Birch, EE. Binocular iPad treatment for amblyopia. Child Vision Research Society 2013; http://cvrsoc.org/docs/CVRS2013-web.pdf; E-Abstract p. 41.
23. Hess RF, Thompson B, Black JM, Machara G, Zhang P, Bobier WR, Cooperstock J. An iPod treatment for amblyopia: An updated binocular approach. *Optometry* 2012; 83: 88–94.
24. Searle A, Norman P, Harrad R, Vedhara K. psychosocial and clinical determinants of compliance with occlusion therapy for amblyopic children. *Eye* 2002; 16: 150–155.
25. Mansouri B, Singh P, Globa A, Pearson P. Binocular training reduces amblyopic visual acuity impairment. *Strabismus* 2014; 22:1–6.
26. Scheiman MM, Hertle RW, Beck RW, Edwards AR, Birch E, Cotter SA, Crouch ER et al. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Arch Ophthalmol* 2005; 123: 437–447.
27. Polat U, Ma-Naim T, Belkint M, Sagi D. Improving vision in adult amblyopia by perceptual learning. *P Natl Acad Sci USA* 2004; 101: 6692–6697.
28. Levi DM, Li RW. Perceptual learning as a potential treatment for amblyopia: a mini-review. *Vision Res* 2009; 49: 2535–2549.